(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 427 680 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 90810854.1

(22) Date of filing: 07.11.90

(51) Int. Cl.5: C07D 498/18, A61K 31/33, //(C07D498/18,311:00,273:00, 221:00)

(30) Priority: 09.11.89 DE 3937336
16.11.89 DE 3938132
23.12.89 DE 3942831
23.12.89 DE 3942833
05.03.90 DE 4006819

(43) Date of publication of application:
15.05.91 Bulletin 91/20

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: SANDOZ LTD.
Lichtstrasse 35
CH-4002 Basel(CH)
(84) BE CH DK ES FR GB GR IT LI LU NL SE

Applicant: SANDOZ-PATENT-GMBH
Humboldtstrasse 3
W-7850 Lörrach(DE)
(84) DE

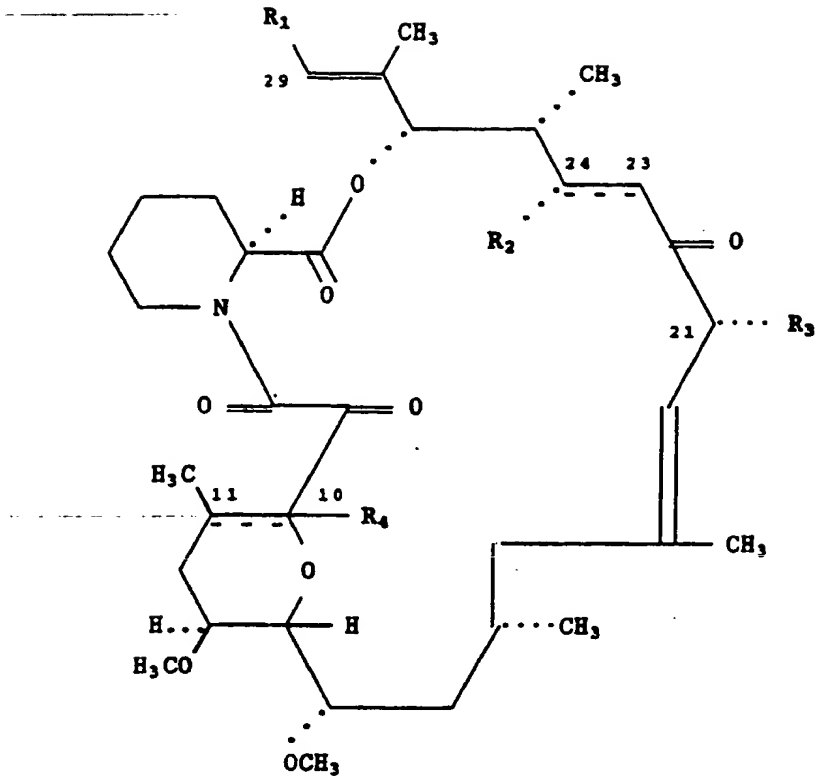
Applicant: SANDOZ-ERFINDUNGEN
Verwaltungsgesellschaft m.b.H.
Brunner Strasse 59
A-1235 Wien(AT)
(84) AT

(72) Inventor: Baumann, Karl
Simmeringer Hauptstrasse 36/2/29
A-1110 Vienna(AT)
Inventor: Emmer, Gerhard
Thereslengasse 25
A-1180 Vienna(AT)

(54) Heteroatoms-containing tricyclic compounds.

(57) The invention concerns the compounds of formula I

EP 0 427 680 A1



I

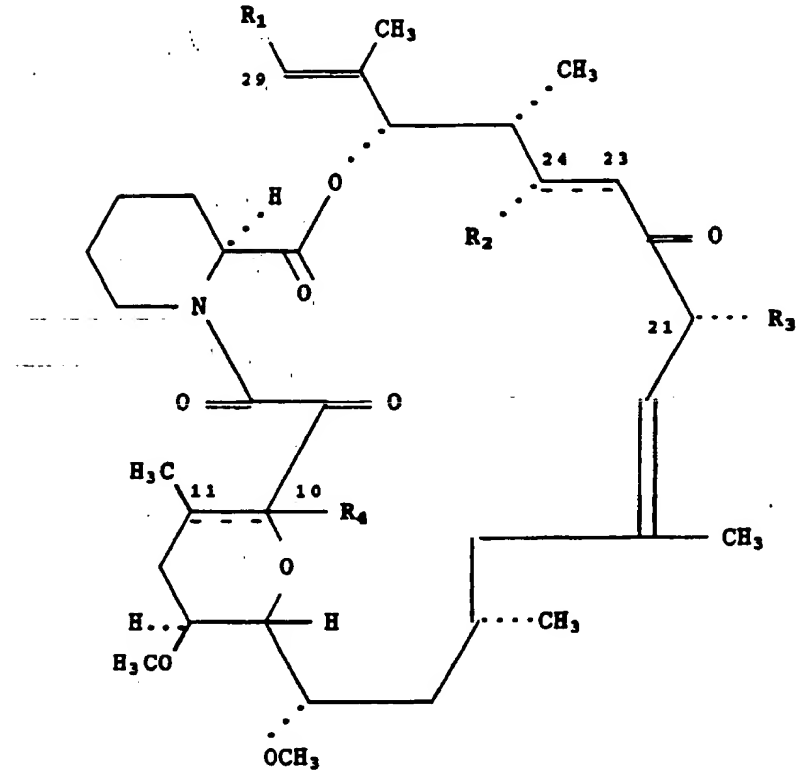
wherein the substituents have various significances.

They are prepared by several processes including epimerizing replacement, treatment with cyanogen bromide or thiophosgene, treatment with an acid having a non-nucleophilic anion, treatment with dimethylsulfoxide and acetic anhydride, acylation, treatment with an oxalyl derivative and ammonia, methylation, oxidation, deprotection and protection.

They possess interesting pharmacological activity as antiinflammatory, immunosuppressant, antiproliferative and chemotherapeutic drug resistance reversing agents.

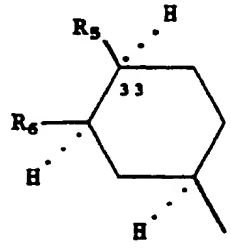
HETEROATOMS-CONTAINING TRICYCLIC COMPOUNDS

The invention relates to the field of macrolides. It concerns the compounds of formula I



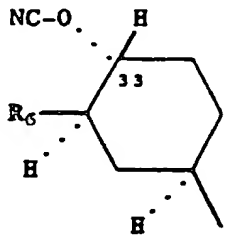
I

wherein
either R_1 is a group (a) of formula



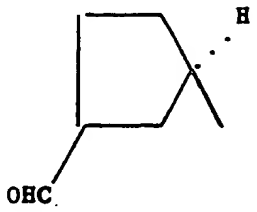
(a)

wherein R_5 is chloro, bromo, iodo or azido and
R_6 is hydroxy or methoxy;
R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydrory and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;
or R_1 is a group (b) or (d) of formula



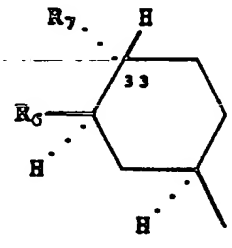
(b)

and



(d)

wherein R_6 is as defined above;
R_2 is as defined above; and
R_4 is hydroxy and there is a single bond in 10,11 position;
or R_1 is a group (c) of formula



(c)

wherein R_6 is as defined above and
R_7 is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; isobutanoyloxy; aminooxalyloxy; R_8R_9CHCOO- wherein R_8 is optionally protected hydroxy or optionally protected amino and R_9 is hydrogen or methyl; or p-tolyloxythiocarbonyloxy;
R_2 is oxo and there is a single bond in 23,24 position; absent and there is a double bond in 23,24 position; or is optionally protected hydroxy, methoxy, methylthiomethoxy, isobutanoyloxy, aminooxalyloxy or R_8R_9CH COO- wherein R_8 and R_9 are as defined above, and there is a single or a double bond in 23,24 position;
whereby for group (c)
1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_2 is other than absent and other than unprotected hydroxy or methoxy, and
there is a single bond in 23,24 position;
2) when R_6 is methoxy and R_7 is methylthiomethoxy
then R_2 is other than absent and other than unprotected hydroxy;
3) when R_6 is methoxy and R_7 is protected hydroxy
then R_2 is other than optionally protected hydroxy; and
4) when R_6 is hydroxy
then R_7 is other than optionally protected hydroxy; and
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is methyl, ethyl, n-propyl or allyl;
in free form and, where such forms exist, in salt form,
hereinafter referred to as "the compounds of the invention".

As is evident from formula I and the definition of the substituents when there is a single bond in 10,11 position the carbon atom to which the methyl group in 11 position is attached has the β-configuration and there is a hydrogen atom with the α-configuration attached to the carbon atom in 11 position; when there is a double bond in 10,11 position this methyl group lies in the plane of the paper and there is no hydrogen atom in 11 position. When R_2 is oxo no hydrogen atom is attached to the carbon atom in 24 position. When R_7 is oxo the hydrogen atom shown in group (c) attached to the same carbon atom as R_7 is absent.

R_1 preferably is a group (c) or (d). R_2 preferably is unprotected hydroxy and there is a single bond in 23,24 position. R_3 preferably is ethyl or allyl. R_4 preferably is hydroxy. R_5 preferably is chloro. R_6 preferably is methoxy. R_7 preferably is isobutanoyloxy, aminooxalyloxy or R_8R_9CHCOO-. R_8 preferably is unprotected hydroxy or unprotected amino, especially unprotected hydroxy. R_9 preferably is hydrogen. When R_9 is other than hydrogen the carbon atom to which it is attached preferably has the (S)

configuration.

Protected hydroxy preferably is hydroxy protected by a conventional hydroxy-protecting group such as formyl, tert-butoxycarbonyl, or trialkylsilyl; it especially is tert-butyldimethylsilyloxy.

Optionally protected hydroxy as defined above under formula I for R_2 and R_7 should not be understood as including a group R_2 or R_7 which is otherwise specified, such as e.g. aminooxalyloxy or R_8R_9CHCOO-.

Protected amino preferably is amino protected by a conventional amino-protecting group such as benzyloxycarbonyl or trialkylsilyl; it especially is tert-butoxycarbonyl.

A compound of the invention preferably is in free form. It preferably is in unprotected form.

A subgroup of compounds of the invention is the **compounds Ip$_1$**, i.e. the compounds of formula I wherein

R_1 is a group (a) wherein R_5 is methoxy and

either R_5 is chloro or bromo and

R_4 is hydroxy and there is a single bond in 10,11 position

or R_5 is azido and

R_4 is hydroxy and there is a single bond in 10,11 position or absent and there is a double bond in 10,11 position;

R_2 is optionally protected hydroxy and there is a single or a double bond in 23,24 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip$_2$**, i.e. the compounds of formula I wherein

R_1 is a group (c) wherein R_6 is methoxy and R_7 is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; aminooxalyloxy; R_8CH_2COO- wherein R_8 is optionally protected amino; or p-tolyloxythiocarbonyloxy;

R_2 is absent and there is a double bond in 23,24 position; or optionally protected hydroxy, methoxy, methylthiomethoxy or aminooxalyloxy and there is a single or double bond in 23,24 position;

whereby

1) when R_7 is oxo, unprotected hydroxy or methoxy

then R_2 is other than absent and other than unprotected hydroxy or methoxy, and

there is a single bond in 23,24 position;

2) when R_7 is methylthiomethoxy

then R_2 is other than absent and other than unprotected hydroxy; and

3) when R_7 is protected hydroxy

then R_2 is other than optionally protected hydroxy; and

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip$_3$**, i.e. the compounds of formula I wherein

R_1 is a group (b) wherein R_6 is methoxy,

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ip$_4$**, i.e. the compounds of formula I wherein

R_1 is a group (d),

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 10,11 position; and

R_3 is as defined above under formula I;

in free form and, where such forms exist, in salt form.

A preferred subgroup of compounds of the invention is the compounds of formula I wherein

R_1 is a group (a) wherein R_5 is as defined above under formula I and R_6 is methoxy;

R_2 is optionally protected hydroxy and there is a single bond in 23,24 position;

R_4 is hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 10,11 position; and

R_3 is ethyl or allyl.

A further preferred group of compounds of the invention is the compounds of formula I wherein
R_1 is a group (b) wherein R_6 is methoxy;
R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is ethyl or allyl.

A further preferred group of compounds of the invention is the compounds of formula I wherein
R_1 is a group (c) wherein R_6 is methoxy and R_7 is as defined above under formula I;
R_2 is oxo and there is a single bond in 23,24 position; or optionally protected hydroxy, methylthiomethoxy, aminooxalyloxy , R_8CH_2COO- wherein R_8 is optionally protected amino, and there is a single or a double bond in 23,24 position;
whereby
1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_2 is other than unprotected hydroxy or methoxy, and there is a single bond in 23,24 position;
2) when R_7 is methylthiomethoxy
then R_2 is other than unprotected hydroxy; and
3) when R_7 is protected hydroxy
then R_2 is other than optionally protected hydroxy;
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is ethyl or allyl.

A further preferred subgroup of compounds of the invention is the compounds of formula I wherein
R_1 is a group (d),
R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is ethyl or allyl.

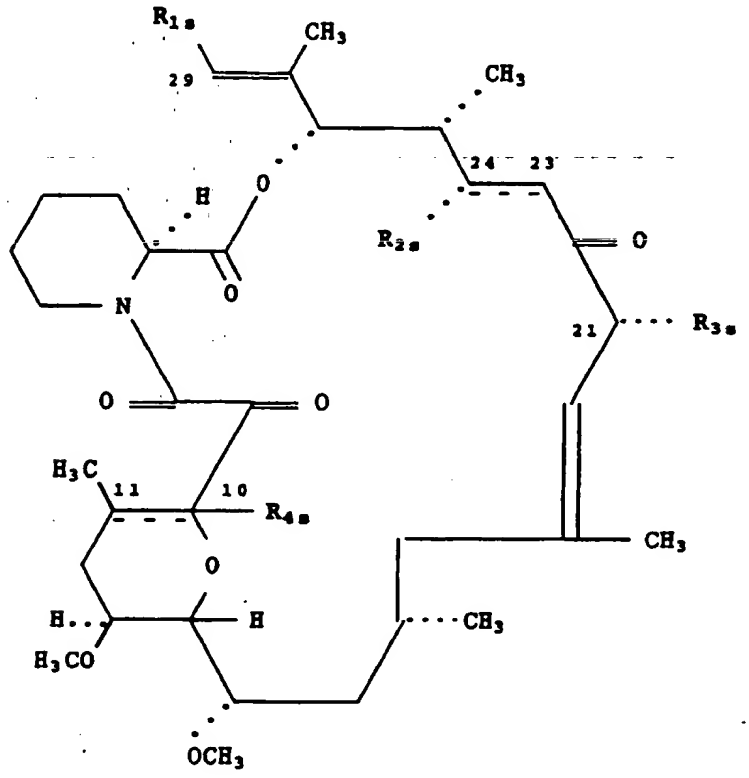
A further subgroup of compounds of the invention is the **compounds Iq**, i.e. the compounds of formula I wherein
either R_1 is a group (a) wherein R_5 is chloro, bromo, iodo or azido and R_6 is hydroxy or methoxy,
R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;
or R_1 is a group (b) or (d) wherein R_6 is hydroxy or methoxy;
R_2 is as defined above for this subgroup; and
R_4 is hydroxy and there is a single bond in 10,11 position;
or R_1 is a group (c) wherein
R_6 is hydroxy or methoxy and
R_7 is aminooxalyloxy; R_8R_9CHCOO- wherein R_8 is optionally protected hydroxy or optionally protected amino and R_9 is hydrogen or methyl; or p-tolyloxythiocarbonyloxy;
R_2 is methylthiomethoxy, isobutanoyloxy, amninooxalyloxy or R_8R_9CHCOO- wherein R_8 and R_9 are as defined above for this subgroup, and there is a single or double bond in 23,24 position;
and
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is methyl, ethyl, n-propyl or allyl,
in free form and, where such forms exist, in salt form.

A further subgroup of compounds of the invention is the **compounds Ir**, i.e. the compounds of formula I wherein
either R_1 is a group (a) as defined above under formula I; and
R_2 and R_4 have the significance indicated above under group (a);
or R_1 is a group (b) or (d) as defined above under formula I; and
R_2 and R_4 have the significance indicated above under groups (b) and (d);
or R_1 is a group (c) as defined above under formula I wherein
R_6 is as defined above under formula I and
R_7 with the exception of optionally protected hydroxy has the significance indicated above under group (c);
whereby for group (c)
1) when R_7 is oxo or methoxy

then R_2 is other than absent and other than methoxy, and there is a single bond in 23,24 position; and
2) when R_6 is methoxy and R_7 is methylthiomethoxy
then R_2 is other than absent; and
R_4 has the significance indicated above under group (c); and
R_3 is as defined above under formula I;
in free form and, where such forms exist, in salt form.

In a subgroup of compounds Ir R_7 is other than oxo or methoxy; in a further subgroup when R_6 is methoxy then R_7 is other than methylthiomethoxy; in a further subgroup R_2 is other than absent and other than methoxy.

A further subgroup of compounds of the invention is the **compounds of formula Is**

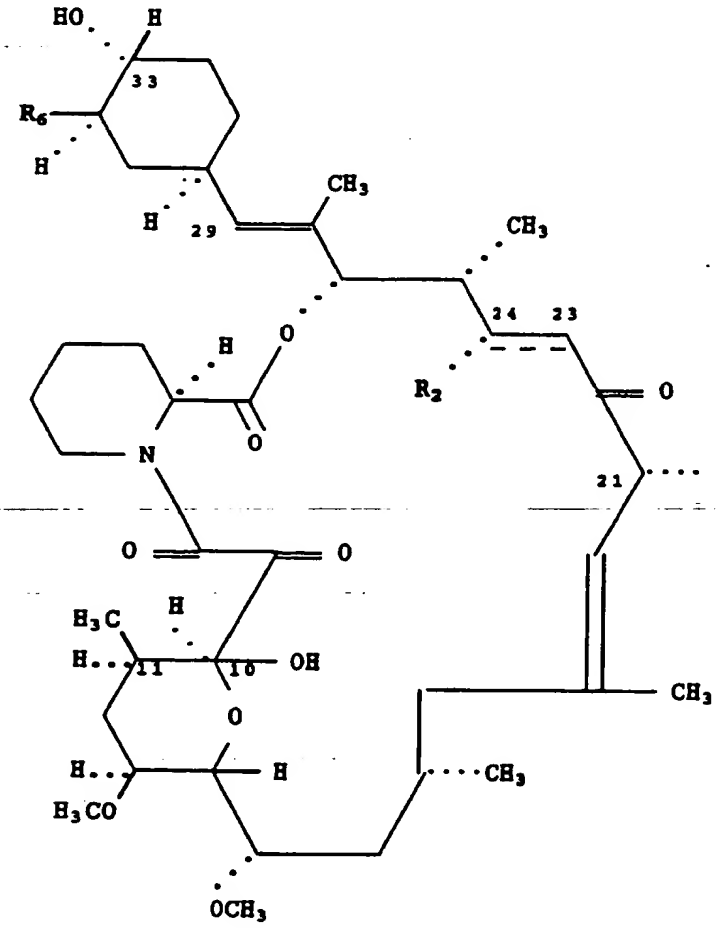


Is

wherein
either R_{1s} is a group (a) wherein R_5 is chloro, bromo, iodo or azido and R_6 is methoxy;
R_{2s} is hydroxy optionally protected by tert-butyldimethylsilyloxy and there is a single bond in 23,24 position; and
R_{4s} is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;
or R_{1s} is a group (b) wherein R_6 is methoxy, or a group (d);
R_{2s} is hydroxy optionally protected by tert-butyldimethylsilyloxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_{4s} is hydroxy and there is a single bond in 10,11 position;
or R_{1s} is a group (c) wherein
R_6 is methoxy and
R_7 is oxo; hydroxy optionally protected by tert-butyldimethylsilyloxy; methoxy; methylthiomethoxy; isobutanoyloxy; aminooxalyloxy; R_8R_9CHCOO- wherein R_8 is hydroxy optionally protected by tert-butyldimethylsilyloxy or amino optionally protected by tert-butoxycarbonyl and R_9 is hydrogen or methyl; or p-tolyloxythiocarbonyloxy;
R_{2s} is oxo and there is a single bond in 23,24 position; absent and there is a double bond in 23,24 position; or is hydroxy optionally protected by tert-butyldimethylsilyloxy, methoxy, methylthiomethoxy, aminoox-

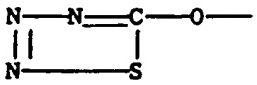
alyloxy or R_8R_9CHCOO- wherein R_8 is amino optionally protected by tert-butoxycarbonyl and R_9 is hydrogen, and there is a single bond in 23,24 position;
whereby for group (c)
1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_{2s} is other than absent and other than unprotected hydroxy or methoxy, and
there is a single bond in 23,24 position;
2) when R_7 is methylthiomethoxy
then R_{2s} is other than absent and other than unprotected hydroxy;
and
3) when R_7 is hydroxy protected by tert-butyldimethylsilyloxy
then R_{2s} is other than hydroxy optionally protected by tert-butyldimethylsilyloxy; and
R_{4s} is hydroxy and there is a single bond in 10,11 position; and
R_{3s} is ethyl or allyl,
in free form and, where such forms exist, in salt form.

A compound of the invention can be obtained by a process comprising
a) for the preparation of a compound of formula I wherein
R_1 is a group (a) as defined above under formula I,
R_2 and R_3 are as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound Ia**),
replacing under simultaneous epimerization the hydroxy group by chlorine, bromine, iodine or azido in a corresponding compound having unprotected hydroxy in 33 position (i.e. a **compound IIa**, of formula IIa



IIa

wherein R_2 and R_3 are as defined above under formula I and
R_6 is hydroxy or methoxy);
b) for the preparation of a compound of formula I wherein
R_1 is a group (b) as defined above under formula I,
R_2 and R_3 are as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound Ib**),
treating a corresponding compound IIa with cyanogen bromide in the presence of a base or
treating a corresponding compound IIa with thiophosgene, reacting the resultant product with an inorganic azide and allowing the resultant unstable intermediate having a group



in 33 position (i.e. a **compound IIb**)
to decompose to a corresponding compound Ib;
c) for the preparation of a compound of formula I wherein
R_1 is a group (d) as defined above under formula I,
R_2 and R_3 are as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound Ic**),
treating a corresponding compound Ib with an acid having a non-nucleophilic anion;
d) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined above under formula I, one of R_2 and R_7 is oxo or methylthiomethoxy and the other is protected hydroxy,
R_3 is as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound Id**),
treating a corresponding compound wherein
one of the substituents in 24 and 33 position is hydroxy and the other is protected hydroxy,
(i.e. a **compound IIc**)
with dimethylsulfoxide and acetanhydride;
e) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein
R_6 is as defined above under formula I and
R_7 is isobutanoyloxy, aminooxalyloxy, R_8R_9CHCOO- as defined above under formula I or p-tolyloxythiocarbonyloxy,
R_2 and R_3 are as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound Ie**),
appropriately acylating a corresponding compound IIa;
f) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein
R_6 is as defined above under formula I and
R_7 is aminooxalyloxy,
R_2 is optionally protected hydroxy or is aminooxalyloxy,
R_3 is as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound If**),
treating with a appropriate oxalyl derivative and thereafter with ammonia a corresponding compound having a optionally protected hydroxy group in 33 position and a protected hydroxy group in 24 position (i.e. a **compound IId**);
g) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined above under formula I,
R_2 and R_7 are as defined above under formula I with the proviso that one of R_2 and R_7 is methoxy,
R_3 is as defined above under formula I and

R_4 is hydroxy
(i.e. a **compound Ig**),
methylating a corresponding compound having a hydroxy group in 24 or 33 position
(i.e. a **compound IIe**);

h) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined above under formula I,
R_2 and R_7 are as defined above under formula I with the proviso that one of R_2 and R_7 is oxo,
R_3 is as defined above under formula I and
R_4 is hydroxy
(i.e. a **compound Ih**),
oxidizing a corresponding compound having a hydroxy group in 24 or 33 position
(i.e. a **compound IIf**); and

- when a resultant compound of formula I has a protected hydroxy and/or a protected amino group, optionally splitting off the protecting group(s) to give a corresponding compound of formula I having one or more unprotected hydroxy and/or unprotected amino group(s)
(i.e. a **compound Ij**),

- whereby when R_1 is a group (a), a water molecule may be simultaneously split off and a compound of formula I is obtained wherein
R_1 is a group (a) as defined above under formula I,
R_2 is unprotected hydroxy and there is a single or double bond in 23,24 position; and
R_4 is absent and there is a double bond in 10,11 position (i.e. a **compound II**); or

- optionally protecting an unprotected hydroxy and/or unprotected amino group in a resultant compound of formula I as appropriate to give a corresponding compound of formula I having one or more protected hydroxy and/or protected amino groups(s) (i.e. a **compound Ik**),

and recovering the resultant compound of formula I in free form and, where such forms exist, in salt form.

The process variants of the invention can be effected in a manner analogous to known procedures.

Process variant a) is a substitution reaction under simultaneous epimerization. It is preferably effected in an inert solvent such as tetrahydrofurane or toluene. Preferably for the substitution by halogen the reaction is effected with tetrachloro-, tetrabromo- or tetraiodomethane in the presence of triphenylphosphine, and for the substitution by azido with azodicarboxylic acid ester, preferably diethyl ester, and hydrazoic acid. A hydroxy group in 24 position may be in protected form. As protecting group known hydroxy protecting groups such as tert-butyldimethylsilyl may be used. A protecting group may subsequently be split off in accordance with known procedures, e.g. with hydrofluoric acid in acetonitrile. Upon deprotection a water molecule may, depending on the reaction conditions chosen, simultaneously be split off in position 10,11 and a double bond formed. The individual compounds can be separated from such a resultant mixture in conventional manner, e.g. chromatographically.

Compounds Ia may be further processed by e.g. oxidation or dehydration to corresponding compounds wherein R_4 is absent; for example, oxidation of compounds Ia wherein R_2 is hydroxy leads to corresponding compounds wherein R_4 is absent and R_2 is oxo.

Process variant b) is a cyanidation reaction. It preferably is effected in an inert solvent such as a chlorinated hydrocarbon, e.g. dichloromethane. The temperature preferably is about room temperature. The base is e.g. 4-dimethylaminopyridine.

A compound of formula I obtained accordance to process variants a) and b) above may be isolated from the reaction mixture and purified in accordance with known methods. When R_2 is hydroxy and there is a single bond in 23,24 position a water molecule may be simultaneously split off. A corresponding mixture of compounds Ib is obtained wherein either R_2 is hydroxy and there is a single bond in 23,24 position or R_2 is absent and there is a double bond in 23,24 position. The individual compounds can be separated from such a resultant mixture in conventional manner, e.g. chromatographically.

The second procedure according to process variant b) is effected by reaction with thiophosgene, preferably in the presence of an acid scavenger such as 4-dimethylaminopyridine. Preferably an inert solvent such as acetonitrile is used. The temperature preferably is about room temperature. The subsequent reaction with a inorganic azide is preferably effected with sodium azide. The resultant compounds IIb are unstable and decompose already at room temperature to compounds Ib, under splitting off of nitrogen and sulfur. This reaction step preferably is effected in an inert solvent such as an aromatic hydrocarbon, e.g. benz ne. Temperature preferably is elevated, e.g. about 50° C.

In process variant c) a ring contraction takes place. Protecting groups which are present may be simultaneously split off. Preferably an inert solvent such as acetonitrile is used. Preferably hydrofluoric acid

is used as acid having a non-nucleophilic anion. Temperature preferably is about room temperature.

Process variant d) is a Swern oxidation. The reaction preferably is effected with compound IIc dissolved in dimethylsulfoxide and acetic anhydride. Duration of reaction is prolonged, e.g. about 5 hours. Temperature preferably is about room temperature.

Process variant e) is an acylation. It is preferably effect d in an inert solvent such as acetonitrile. The acylating agent preferably is an activated acyl derivative, such as a acyl halogenide or anhydride. An acid scavenger such as dimethylaminopyridine or pyridine is employed. Further, a compound IIa may also be reacted with a carboxylic acid such as glycine protected at the amino moiety by e.g. tert-butoxycarbonyl, or with a compound of formula $R_8R_9CHCOOH$ wherein R_8 is protected hydroxy and R_9 is hydrogen or methyl, and a carbodiimide such as N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide or N,N'-dicyclo-hexylcarbodiimide, where indicated in the presence of a base, such as 4-dimethylaminopyridine, preferably in an inert solvent such as acetonitrile or in a chlorinated hydrocarbon. An amino protecting group may subsequently be split off together with any hydroxy protecting group which may be present. If in the starting compound IIa R_2 is hydroxy and there is a single bond in 23,24 position, upon acylation splitting off of a water molecule in 23,24 position may occur and a compound Ie be formed wherein R_2 is absent and there is a double bond in 23,24 position.

Process variant f) is an acylation. It is preferably effected in an inert solvent such as acetonitrile. Temperature preferably is reduced, e.g. about 0 to 5°C. The oxalyl derivative preferably is an oxalyl halogenide, e.g. chloride. Upon completion of the reaction the mixture is stirred with ammonia.

Process variant g) is a methylation. It preferably is effected in an inert solvent such as a chlorinated hydrocarbon, e.g. dichloromethane. The methylating agent preferably is diazomethane in the presence of e.g. borotrifluoride-etherate. Temperature preferably is from about 0° to about room temperature.

Process variant h) is an oxidation. The oxidizing agent is e.g. tetrapropylammonium perruthenate. The temperature preferably is about room temperature.

The optional deprotection process variant may also be effect in conventional manner. For splitting off of e.g. tert-butyldimethylsilyl it is effected by treatment with e.g. hydrofluoric acid in a solvent such as acetonitrile. Depending on the reaction conditions selected (duration, temperature, etc.) the splitting can be steered in such a manner that either all or only some protecting group are removed. Partial deprotection is particularly indicated where a definite hydroxy group is to be subsequently reacted in a later reaction.

The optional protection step variant may also be effected in conventional manner along similar lines.

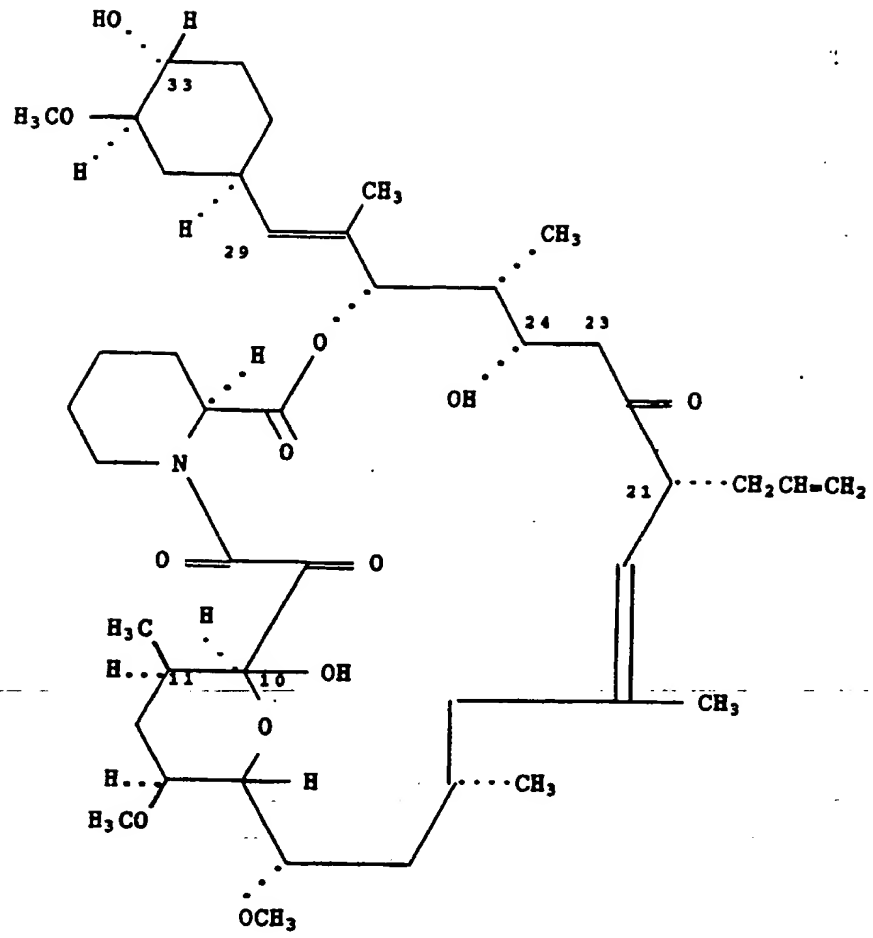
Thus for subsequent reactions involving a hydroxy group, particularly a hydroxy group in position 24 and/or 33, selective protection of only one of the two free hydroxy groups or selective deprotection of only one of the two protected hydroxy groups may be effected in such a manner that reaction occurs only at the desired position. Mixtures of end products may be obtained thereby; such mixtures can be separated in conventional manner, e.g chromatographically. Resultant end products still containing protecting groups can be subsequently deprotected. Reaction conditions may alternatively be selected such that simultaneously with or immediately after reaction the protecting groups are removed (one pot process).

The compounds of formula I may be isolated and purified from the reaction mixture in conventional manner.

Insofar as their preparation is not specifically described herein, e.g. in the Examples; the compounds used as starting materials are known or can be obtained in conventional manner from known compounds, e.g. starting from appropriate Streptomyces strains such as Streptomyces tsukubaensis No. 9993 described in e.g. Fujisawa EP 184162. Samples can be obtained from the Fermentation Research Institute, Tsukuba, Ibaraki 305, Japan under provisions of the Budapest Treaty under deposit No. FERM BP-927. This strain has been redeposited on April 27, 1989 e.g. as disclosed in Sandoz EP 356399, with the Agricultural Research Culture Collection International Depository, Peoria, Illinois 61604, USA under the provisions of the Budapest Treaty under deposit No. NRRL 18488.

The following Examples illustrate the invention and are not limitative. All temperatures are in degrees Centigrade. All NMR spectra are in $CDCl_3$, ppm. The abbreviations have the following meanings:

BOC: tert-butoxycarbonyl;
cfr: colourless foamy resin:
db: double bond;
Et: ethyl;
FK 506: the compound of formula



i.e. 17α-allyl-1β,14α-dihydroxy-12-[2′-(4″(R)-hydroxy-3″(R)-methoxycyclohex-1″(R)-yl)-1′-methyl-trans-vinyl]-23α,25β-dimethoxy-13α,19,21α,27β-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-trans-ene-2,3,10,16-tetraone (according to the atom numbering in EP 184162; however, in the Examples the atom numbering of formula I is used throughout);
FR 520: as FK 506, but with ···CH_2CH_3 (ethyl) in place of allyl in position 21 in the formula;
iBuoyloxy: isobutanoyloxy [$(H_3C)_2CHCOO$-];
iPr: isopropyl;
na: not applicable;
N_3: azido;
OMe (or MeO): methoxy;
OtBDMS: tert-butyldimethylsilyloxy;
sb: single bond;
tBu: tert-butyl.

Example 1: 24-tert-Butyldimethylsilyloxy-33-epi-33-chloro-FK506

[Formula 1: R_1 = a group (a) wherein R_5 = chloro, R_6 = OMe; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant a), r placement with epimerization]

0.092 g **24-tert-butyldimethylsilyloxy-FK506** is heated for 15 hours under refluxing with 0.037 g triphenylphosphine in 4 ml of tetrachloromethane. The solvent is evaporated to dryness under reduced pressure and the residue is purified by column chromatography over silicagel using a mixture of hexane and acetic acid ethyl ester (2:1) as the eluant. The **title compound** is obtained (colourless foam):
^{1}H-NMR: about 2:3 mixture of conformers:
main conformer: 4.56 (m, $w_{1/2}$ = 7 Hz, H-33).

The starting material is obtained as follows:

a) 20 g **FK 506** is dissolved in 400 ml of dry dimethylformamide, 5.08 g imidazole and 11.25 g tert-butyldimethylchlorosilane is added in portions and the mixture is stirred for 110 hours at room temperature. The reaction mixture is diluted with acetic acid ethyl ester and washed five times with water. The organic phase is dried over sodium sulfate and the solvent distilled off under reduced pressure. The resultant crude product is purified by chromatography over silicagel using hexane/acetic acid ethyl ester 3:1 as the eluant. **24,33-Bis-(tert-butyldimethylsilyloxy)-FK 506** is obtained:
^{13}C-NMR: main conformer: 69.7 (C-24); 75.1 (C-33); 84.1 (C-32); 164.6 (C-8); 168.9 (C-1); 196.4 (C-9); 209.3 (C-22);
minor conformer: 70.9 (C-24); 75.3 (C-33); 84.1 (C-32); 165.8 (C-8); 168.2 (C-1); 191.2 (C-9); 210.0 (C-22);

b) 0.5 g 24,33-bis-(tertbutyldimethylsilyloxy)-FK506 is dissolved at 0° under stirring into a mixture of 10 ml of acetonitrile and 0.5 ml of 40 % hydrofluoric acid. After 2 hours at that temperature the reaction medium is diluted with dichloromethane. The solution is successively washed with saturated aqueous sodium bicarbonate solution and water and the organic phase is dried over sodium sulfate, and the solvent is evaporated under reduced pressure. The resultant residue is purified by column chromatography over silicagel (eluant: dichloromethane/methanol 9:1). **24-tert-Butyldimethylsilyloxy-FK 506** is obtained as a colourless foam:
^{13}C-NMR: main conformer: 69.7 (C-24); 73.6 (C-33); 84.1 (C-32); 164.6 (C-8); 168.9 (C-1); 196.4 (C-9); 209.2 (C-22);
minor conformer: 70.7 (C-24); 73.6 (C-33); 84.2 (C-32); 165.8 (C-8); 168.2 (C-1); 191.4 (C-9); 209.2 (C-22).

Example 2: 24-tert-Butyldimethylsilyloxy-33-epi-33-azido-FK506

[Formula I: R_1 : a group (a) wherein R_5 : azido, R_6 : OMe; R_2 : OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant a)]

To a solution of 0.092 g **24-tert-butyldimethylsilyloxy-FK506** and 0.08 g triphenylphosphine in 2 ml of dry tetrahydrofurane is added at 0° 0.047 ml of azodicarboxylic acid diethyl ester, followed by 0.15 ml of a 2 M solution of hydrazoic acid in toluene. The solution is brought to room temperature and stirred for 18 hours. The solvent is evaporated to dryness under reduced pressure and the residue purified as described above under Example 1. The **title compound** is obtained (colourless foam):
^{1}H-NNR: 4.07 (m, H-33).

The following compounds of formula I are obtained in analogous manner in accordance with process variant a):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
3	1[1)]	(a)	Cl	OMe	na	OtBDMS	sb	Et	OH	sb	NMR*
4	1[1)]	(a)	Br	OMe	na	OtBDMS	sb	Et	OH	sb	
5	1	(a)	Br	OMe	na	OtBDMS	sb	allyl	OH	sb	
6	2[1)]	(a)	N_3	OMe	na	OtBDMS	sb	Et	OH	sb	
6a	1[1)]	(a)	I	OMe	na	OtBDMS	sb	Et	OH	sb	NMR*

*NMR: Example 3: ^{1}H-NMR: 4.56 (m, H-33);
Example 6a: ^{13}C-NMR: mixture of conformers: 210.33 (C-22); 168.91 (C-1); 164.59 (C-8); 123.64 (C-20); 78.90 (C-32); 25.81 (tBu);

1) The starting material is obtained from FR 520 in a manner analogous to 24-tert-butyldimethylsilyloxy-FK 506 (see Example 1):
a) 24,33-bis-(tert-butyldimethylsilyloxy)-FR 520: ^{1}H-NMR: about 2:1 mixture of 2 conformers:
main conformer: 4.42 (m, H-2); 4.41 (db, 13 Hz, H-6 eq.); 4.05 (txt, J=1.5 Hz and 6 Hz, H-24); 3.80 (dxd, J=1.5 Hz and 10 Hz, H-14); 2.95 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32);
minor conformer: 4.25 (q, J=5 Hz, H-24); 3.94 (dxd, J=2 Hz and 10 Hz, H-14); 2.95 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32);

EP 0 427 680 A1

b) 24-tert-butyldimethylsilyloxy-FR 520: ^{1}H-NMR: about 2:1 mixture of 2 conformers:
main conformer: 4.44 (b, H-2); 4.42 (db, J=13 Hz, H-6 eq.); 4.05 (dxt, J=1,5 Hz and 6 Hz, H-24); 3.81 (dxd, J=1.5 Hz and 10 Hz, H-14); 3.01 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32);
minor conformer: 4.24 (H-24); 3.94 (dxd, J=2 Hz and 10 Hz, H-14); 3.01 (dxdxd, J=4 Hz, 8 Hz and 11 Hz, H-32).

Example 7: 24-tert-Butyldimethylsilyloxy-33-cyanoxy-FR 520

[Formula I: R_1 = a group (b) wherein R_6 = OMe; R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant b), treatment with cyanogen bromide]

A solution of 2 g **24-tert-butyldimethylsilyloxy-FR 520** and 0.94 g 4-dimethylaminopyridine in 100 ml of dichloromethane is rapidly reacted at room temperature with a solution of 0.4 g cyanogen bromide in 15 ml of dichloromethane and the mixture is stirred at room temperature for 20 minutes. The mixture is filtered over silicagel (eluant: n-hexane/acetic acid ethyl ester) and the solvent is removed from the relevant fraction under reduced pressure. The **title compound** is obtained as a colourless foamy resin:
^{1}H-NMR: mixture of conformers: 4.3 (m; H-33).

Example 8: 24-tert-Butyldimethylsilyloxy-33-cyanoxy-FR 520

[Formula I: as for Example 7]

[Process variant b), treatment with thiophosgene and sodium azide]

A solution of 2 g **24-tert-butyldimethylsilyloxy-FR 520** and 2 g 4-dimethylaminopyridine in 50 ml of acetonitrile is carefully reacted with 0.4 ml of thiophosgen and the mixture stirred for 3 hours at room temperature. The reaction mixture is poured onto a well-stirred mixture consisting of 150 ml of acetic acid ethyl ester, 40 ml of saturated aqueous sodium chloride solution and 50 ml of 2 N sodium azide solution, vigourous stirring is continued for 5 minutes and the organic phase is separated. The organic phase is then successively washed with water, 1 N hydrochloric acid solution, water, and saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is taken up in about 100 ml of benzene and heated at 30-40° for 2 hours. The benzene is removed under reduced pressure and the **title compound** is recovered from the residue as a colourless foamy resin by column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):
^{1}H-NMR: see Example 7.

The following compounds of formula I are obtained in analogous manner in accordance with process variant b):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
9	7,8	(b)	na	OMe	na	OtBDMS	sb	allyl	OH	sb	NMR*
10a[1)]	7,8	(b)	na	OMe	na	OH	sb	Et	OH	sb	NMR*
10b[1)]	7,8	(b)	na	OMe	na	absent	sb	Et	OH	sb	NMR*
11a[2)]	7,8	(b)	na	OMe	na	OH	sb	allyl	OH	sb	
11b[2)]	7,8	(b)	na	OMe	na	absent	sb	allyl	OH	sb	

*NMR: Example 9: ^{1}H-NMR: mixture of conformers: 4.3 (m, H-33);
Example 10a: ^{1}H-NMR: mixture of conformers: 5.34 (H-26); 4.63 (db, J = 4 Hz, H-2); 4.44 (db, J = 13 Hz, H-6 eq.); 4.30 (dxdxd, J = 5 Hz, 8 Hz and 11 Hz, H-33); 3.01 (tb, J = 13 Hz, H-6ax.);
Example 10b: ^{1}H-NMR: 6.81 resp. 6.75 (dxd resp. dxd, J = 5 Hz and 15 Hz resp. 7 Hz and 15 Hz, H-24); 6.2 resp. 6.3 (dxd resp. dxd. J = 2 Hz and 15 Hz resp. 1 Hz and 15 Hz, H-23); 5.29 resp. 5.23 (d resp. d, J = 3 Hz resp. 3 Hz, H-26); 4.3 (m, H-3);
[1)2)] A mixture of both compounds is obtained; they can be separated chromatographically (eluant: n-hexane/acetic acid ethyl ester).

Example 12: 29-Des-(4-hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520

[Formula I: R_1 = a group (d); R_2 = OH, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant c), treatment with a non-nucleophilic anion]

0.5 g **24-tert-butyldimethylsilyloxy-33-cyanoxy-FK 520** (compound of Examples 7 and 8) or **33-cyanoxy-FR 520** (compound of Example 10a) is dissolved into a mixture of 50 ml of acetonitrile and 2 ml of 40 % wt. aqueous hydrofluoric acid and the mixture is stirred for 2.5 hours at room temperature. The reaction mixture is then distributed between acetic acid ethyl ester and saturated aqueous sodium bicarbonate solution, the aqueous phase is discarded and the organic phase is washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained as a colourless foamy resin from the residue by column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):
^{1}H-NMR: mixture of conformers: 9.64 (d, J = 2 Hz, CHO); 2.87 (m, H-32); 2.67 (m, H-30).

The following compounds of formula I are obtained in analogous manner in accordance with process variant c):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
13	12[1)]	(d)	na	na	na	OH	sb	allyl	OH	sb	NMR*
14	12[2)]	(d)	na	na	na	absent	db	Et	OH	sb	NMR*

*NMR: Example 13: ^{1}H-NMR: mixture of conformers: 9.65 (d, J = 2 Hz, CHO); 2.86 (m, H-32); 2.15 (dxdxd, J = 12.5 Hz and 7.5 Hz and 5 Hz, H-31a); 1.45 (dxt, J = 12.5 and 9 Hz, H-31b); 2.67 (m, H-30); Example 14: ^{1}H-NMR: about 5:3 mixture of conformers: 9.66 (d, J = 2 Hz, CHO); 6.83 (dxd, J = 15 and 5 Hz) resp. 6.77 (dxd, J = 15 and 7.5 Hz) H-24; 6.19 (dxd, J = 15 and 1.5 Hz) resp. 6.30 (dxd, J = 15 and 1 Hz) H-23;

1) Starting from the compound of Example 9 or 11a;

2) Starting from the compound of Example 10b.

Example 15:

a) 24-tert-Butyldimethylsilyloxy-33-oxo-FK 506
and
b) 24-tert-Butyldimethylsilyloxy-33-methylthiomethoxy FK 506

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = oxo and, respectively, methylthiomethoxy; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant d), treatment with dimethylsulfoxide and acetanhydride]

1 g **24-tert-Butyldimethylsilyloxy-FK 506** is dissolved at room temperature into a mixture of 20 ml of acetanhydride and 30 ml of dimethylsulfoxide and stirring is effected for 5 hours at room temperature. The reaction mixture is poured onto a mixture of acetic acid ethyl ester and potassium carbonate solution, stirred for 20 minutes, the phases are separated and the organic phase is repeatedly washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. Following column chromatographic fractionation of the residue over silicagel (eluant: acetic acid ethyl ester / n-hexane 2:1) the **title compounds** are obtained as colourless foamy resins:

compound a): ^{13}C-NMR: about 2:1 mixture of conformers:
209.3/209.9 (C-22); 208.3/208.5 (C-33); 196.4 (C-9); 168.9/168.2 (C-1); 164.6/165.9 (C-8); 138.5/139.4 (C-19); 135.6/136.1 (C-37); 133.4/134.1 (C-28); 131.8/127.6 (C-29); 123.1/122.3 (C-20); 116.5/116.1 (C-38); 97.6/98.9 (C-10); 83.0 (C-32); 69.6/70.6 (C-24);
compound b): ^{1}H-NMR: about 2:1 mixture of conformers:
4.82/4.79 (AB; J_{AB} = 12 Hz; -O-CH_2-S); 2.19 resp. 2.18 (s resp. s, -SCH_3);

The following compounds of formula I are obtained in analogous manner in accordance with process variant d):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
16a	15[1)]	(c)	na	OMe	OtBDMS	OCH_2SCH_3	sb	allyl	OH	sb	cfr; NMR*
16b	15[1)]	(c)	na	OMe	OtBDMS	oxo	sb	allyl	OH	sb	cfr; NMR*
16c	15[2)]	(c)	na	OMe	oxo	OtBDMS	sb	Et	OH	sb	cfr
16d	15[3)]	(c)	na	OMe	OtBDMS	oxo	sb	Et	OH	sb	cfr

[1)] Starting from 33-tert-butyldimethylsilyloxy-FK 506 (compound of Example 16 in EP 184162); eluant: toluene / acetic acid ethyl ester 9:1;
[2)] Starting from 24-tert-butyldimethylsilyloxy-FR 520;
[3)] Starting from 33-tert-butyldimethylsilyloxy-FR 520 (DOS 39 38 754);
*NMR: Example 16a: ^{1}H-NMR: about 2:1 mixture of conformers: 4.36 (s, -O-CH_2-S) and 2.16 (s, -SCH_3) resp. 4.37 and 4.40 (AB, -O-CH_2-S) and 2.13 (s, -SCH_3);
Example 16b: ^{1}H-NMR: about 1:1 mixture of conformers: 5.29 and 5.59 (s, H-23);
^{13}C-NMR: about 1:1 mixture of conformers: 200.7/197.7 (C-22); 195.3/194.9 (C-24); 193.2/189.6 (C-9); 168.9/169.1 (C-1); 164.4/165.2 (C-8); 137.5/137.9 (C-19); 135.1/135.3 (C-37); 130.1/131.1 (C-24); 130.1/129.3 (C-28); 123.9/123.7 (C-20); 16.7/116.7 (C-38); 98.7/98.0 (C-10); 96.3/97.8 (C-23).

Example 17: 33-p-Tolyloxythiocarbonyloxy-FK 506

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = p-tolyloxythiocarbonyloxy; R_2 = OH, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant e), acylation]

A solution of 2 g **FK 506** in 70 ml of acetonitrile is successively reacted with 0.46 g 4-dimethylaminopyridine and 1.8 g p-tolyloxythiocarbonyl chloride and the mixture is stirred for 15 hours at room temperature. The reaction mixture is then diluted with acetic acid ethyl ester and successively washed with saturated aqueous sodium bicarbonate solution, 0.5 N hydrochloric acid and water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is isolated from the residue as a light yellow foamy resin by column chromatography over silicagel (eluant: acetic acid ethyl ester / n-hexane 1:1):
^{1}H-NMR: 7.22 and 7.01 (AABB-syst., ar-H); 5.35 (d, J = 1 Hz, H-26); 5.18 (dxdxd, J = 5 Hz, 9.5 Hz and 11 Hz, H-33); 3.475, 3.47, 3.41, 3.40, 3.355 and 3.32 (each s, -OCH_3); 2.38 (s, ar-CH_3);

Example 18: 33-Aminomethylcarbonyloxy-Δ^{23}-FK 506

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = R_8R_9CHCOO-(R_8 = amino; R_9 = H); R_2 = absent, double bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant e)]

2 g N-BOC-glycine, 1 g dicyclohexylcarbodiimide, 0.5 g Δ^{23}-**FK 506** (second compound of Example 17 in EP 184162) and 1 g 4-dimethylaminopyridine are successively taken up at room temperature in 70 ml of acetonitril and the mixture is stirred for 20 minutes at room temperature. The reaction mixture is filtered, the filtrate diluted with acetic acid ethyl ester and successively washed with 1 N hydrochloric acid, aqueous

sodium bicarbonate solution and water, the organic phase is dried over sodium sulfate, filtered, concentrated, and the **residue** is taken up in 50 ml of acetonitrile.

In order to split off the protecting group 0.5 g p-toluenesulfonic acid monohydrate is added and the mixture heated to refluxing for 5 minutes, the solution is cooled off, diluted with acetic acid ethyl ester, washed to neutrality with water, the organic phase is dried over sodium sulfate and concentrat d. From th residue the **title compound** is obtained as a colourless foamy resin after column chromatography over silicagel (eluant: acetic acid ethyl ester / methanol 20:3):

^{1}H-NMR: about 6:5 mixture of conformers:

6.81 (dxd, J = 5 Hz and 15 Hz) resp. 6.76 (dxd, J = 75 Hz and 15 Hz) H-24; 6.18 (dxd, J = 1 Hz and 15 Hz) resp. 6.29 (dxd, J = 1 Hz and 15 Hz) H-23; 4.77 (m, H-33);

Example 19: 24-tert-Butyldimethylsilyloxy-FR 520-33-[(tert-butyldimethylsilyloxy)-(S)-lactate]

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = R_8R_9CHCOO-(R_8 = OtBDMS, R_9 = Me, S-configuration); R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant e)]

To a solution of 450 mg **24-tert-butyldimethylsilyloxy-FR 520** and 120 mg tert-butyldimethylsilyloxy-(S)-lactic acid in 10 ml of dichloromethane are added at room temperature 120 mg N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride and 23 mg dimethylaminopyridine. After 60 hours the reaction mixture is diluted with acetic acid ethyl ester, washed successively with 0.5 N hydrochloric acid and then water, dried over sodium sulfate, filtered, and the solvent is evaporated under reduced pressure. The residue is chromatographed over silicagel (eluant: n-hexane / acetic acid ethyl ester 2:1). The **title compound** is obtained as a colourless foam:

^{1}H-NMR: 1.41 (d, J = 7 Hz); 4.34 [q, J = 7 Hz, -COCH(CH_3)OSi]; 4.75 (m, H-33).

Example 20: FK 506-33-glycolate

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = R_8R_9CHCOO- (R_8 = OH, R_9 = H); R_2 = OH, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant e)]

To a solution of 300 mg tert-butyldimethylsilyloxymethylcarboxylic acid in 5 ml of dichloromethane are added under stirring at 0° 0.67 ml of oxalyl chloride and one drop of dimethylformamide. The mixture is brought to room temperature and is stirred for 1 hour. The reaction mixture is concentrated under reduced pressure. The residue is taken up in 5 ml of dichloromethane and this solution is added dropwise at 0° to a solution of 600 mg **FK 506**, 0.28 ml triethylamine and a catalytic quantity of 4-dimethylaminopyridine. After 18 hours stirring at 0° the solution is diluted with acetic acid ethyl ester, successively washed with 0.1 N hydrochloric acid and water, the organic phase is dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue is taken up in 20 ml of acetonitrile, reacted with 0.5 ml of 40 % wt. aqueous hydrofluoric acid and stirred for 20 minutes at room temperature. The mixture is diluted with acetic acid ethyl ester, washed with saturated aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained as a colourless foamy resin from the residue by chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):

^{1}H-NMR: 4.13 (s, -COCH$_2$OH); 4.41 (d, br, J = 13 Hz, H-6e); 4.60 (d, br, J = 4 Hz, H-2); 4.78 (m, H-33); 5.16 + 5.30 (H-26).

The following compounds of formula I are obtained in analogous manner in accordance with process variant e):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
21	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	OtBDMS	sb	allyl	OH	sb	cfr; NMR*
22	17 to 20	(c)	na	OMe	tBDMS-OCH_2COO-	OtBDMS	sb	allyl	OH	sb	cfr; NMR*
23	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	OtBDMS	sb	Et	OH	sb	cfr
24	17 to 20	(c)	na	OMe	tBDMS-OCH_2COO-	OtBDMS	sb	Et	OH	sb	cfr; NMR*
25a	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	OH	sb	allyl	OH	sb	cfr; NMR*
25b	17 to 20	(c)	na	OMe	OH	BOC-$NHCH_2COO$-	sb	allyl	OH	sb	cfr; NMR*
25c	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	BOC-$NHCH_2COO$-	sb	allyl	OH	sb	cfr; NMR*
25d	17,19,20	(c)	na	OMe	BOC-$NHCH_2COO$-	absent	db	allyl	OH	sb	cfr;
26a	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	OH	sb	Et	OH	sb	cfr
26b	17 to 20	(c)	na	OMe	OH	BOC-$NHCH_2COO$-	sb	Et	OH	sb	cfr
26c	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	BOC-$NHCH_2COO$-	sb	Et	OH	sb	cfr
26d	17 to 20	(c)	na	OMe	BOC-$NHCH_2COO$-	absent	db	Et	OH	sb	cfr
27a	17 to 20	(c)	na	OMe	NH_2COCOO-	OH	sb	allyl	OH	sb	cfr
27b	17 to 20	(c)	na	OMe	NH_2COCOO-	NH_2COCOO-	sb	allyl	OH	sb	cfr; NMR*
27c	17 to 20	(c)	na	OMe	NH_2COCOO-	absent	db	allyl	OH	sb	cfr
28a	17 to 20	(c)	na	OMe	NH_2COCOO-	OH	sb	Et	OH	sb	cfr; NMR*
28b	17 to 20	(c)	na	OMe	NH_2COCOO-	NH_2COCOO-	sb	Et	OH	sb	cfr
28c	17 to 20	(c)	na	OMe	NH_2COCOO-	absent	db	Et	OH	sb	cfr
29	17 to 20	(c)	na	OMe	NH_2COCOO-	OtBDMS	sb	Et	OH	sb	cfr; NMR*
30	17 to 20	(c)	na	OMe	NH_2COCOO-	OtBDMS	sb	allyl	OH	sb	cfr
31	17 to 20	(c)	na	OMe	p-tolyloxy-thiocarbonyloxy	OH	sb	Et	OH	sb	cfr; NMR*
32	17 to 20	(c)	na	OMe	$HOCH_2COO$-	OH	sb	Et	OH	sb	cfr; NMR*

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
33	17 to 20	(c)	na	OMe	tBDMS-OCH(CH_3)COO- (S)	OH	sb	Et	OH	sb	cfr
34	17 to 20	(c)	na	OMe	iBuoyloxy	OtBDMS	sb	Et	OH	sb	cfr; NMR*
35	17 to 20	(c)	na	OMe	iBuoyloxy	OtBDMS	sb	allyl	OH	sb	cfr
36	17 to 20	(c)	na	OMe	iBuoyloxy	OH	sb	allyl	OH	sb	cfr
37	17 to 20	(c)	na	OMe	iBuoyloxy	OH	sb	Et	OH	sb	cfr; NMR*
38	17,18,20	(c)	na	OMe	tBDMS-OCH(CH_3)COO- (S)	OtBDMS	sb	Et	OH	sb	cfr; NMR*

*^{1}H-NMR: Example 21: mixture of conformers: 4.85 (m, H-33); 3.93 (s, O=C-CH_2-N-); 3.22 (m, H-32);

^{1}H-NMR: Example 22: 4.25 (s, -$COCH_2OSi$); 4.76 (m, H-33);

^{1}H-NMR: Example 24: 4.26 (s, -$COCH_2OSi$);

^{1}H-NMR: Example 25a: 5.7 (m, H-37); 4.75 (dxdxd, J=5 Hz, 9 Hz and 10 Hz, H-33); 3.93 (m, N-CH_2-); 1.46 (s, tBu);

^{1}H-NMR: Example 25b: mixture of conformers: 5.69 (m, H-37); 4.52 (H-2); 4.44 (H-6 eq.); 3.87 (m, -N-CH_2-C=O); 1.46 (s, N-BOC);

^{1}H-NMR: Example 25c: 5.7 (m, H-37); 4.76 (dxdxd, J=5 Hz, 8 Hz and 10 Hz, H-33); 3.93/3.87 (m/m, -N-CH_2); 1.46 (s, tBu);

^{1}H-NMR: Example 27b: about 2:1 mixture of conformers: 7.15-7.0 and 6.1-6.2 (b, each 2H, O=C-NH_2); 5.28 and 5.42 (q/q, J=5 and 5 Hz, H-24); 4.84 (m, H-33);

^{1}H-NMR: Example 28a: mixture of conformers: 7.01 and 5.98 (-$CONH_2$); 5.35 (d, J=1 Hz, H-26); 4.85 (m, H-33); 4.61 (db, J=3 Hz, H-2); 4.44 (db, J=13 Hz, H-6 eq.);

^{1}H-NMR: Example 29: mixture of conformers: 7.03 and 6.12 ($CONH_2$); 4.85 (m, H-33); 4.45 (H-2); 4.42 (H-6 eq.); 0.88 (s, tBu); 0.04 (s, Si-CH_3);

EP 0 427 680 A1

^{1}H-NMR:	Example 31:	mixture of conformers: 7.22/7.02 (AA'BB'-syst., ar-H); 5.35 (d, J=1 Hz, H-26); 5.18 (m, H-33); 4.63 (db, J=4 Hz, H-2); 4.45 (db, J=13 Hz, H-6 eq.); 2.37 (s, ar-CH_3);
^{1}H-NMR:	Example 32:	4.13 (s, -$COCH_2OH$); 4.40 (d, br, J=13 Hz, H-6e); 4.58 (d, br, J=4 Hz, H-2); 4.78 (m, H-33); 5.17 + 5.30 (H-26);
^{1}H-NMR:	Example 34:	4.69 (m, H-33); 2.55 [septet, J=7 Hz, O=C-$CH(CH_3)_2$]; 1.17 [d, J=7 Hz, $C(CH_3)_2$];
^{1}H-NMR:	Example 37:	4.68 (dxdxd, J=5 Hz, 10 Hz and 11 Hz, H-33); 2.55 [septet, J=7 Hz, O=C-$CH(CH_3)_2$]; 1.17 [d, J=7 Hz, $C(CH_3)_2$]; Minor component: 1.23 (d, J=7 Hz; 4.30 [dq, J_1=5 Hz, J_2=7 Hz, -$COCH(CH_3)OH$]; 4.78 (ddd, J_1=5 Hz, J_2= 9 Hz, J_3= 11 Hz, H-33); 5.20 (H-26);
^{1}H-NMR:	Example 38:	see Example 19.

Example 39: 24-tert-Butyldimethylsilyloxy-33-aminooxalyloxy-FK 506

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = aminooxalyloxy; R_2 = OtBDMS, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant f), treatment with oxalyl chloride and ammonia]

A solution of **24,33-bis-(tert-butyldimethylsilyloxy)-FK 506** in 70 ml of acetonitrile is reacted at 0° to 5° with 1 ml of oxalyl chloride and stirred at 0 to 5° for 40 minutes. The reaction mixture is stirred with a mixture of acetic acid ethyl ester and satured aqueous ammonia solution, any precipitate formed is sucked off, the phases are separated, the organic phase is washed successively with 1 N hydrochloric acid and then water, dried over sodium sulfate, filtered and concentrated under reduced pressure. From the residue the **title compound** is obtained as a colourless foamy resin following column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester 1:1):

^{1}H-NMR: about 2:1 mixture of conformers:

7.04 and 6.17 (b, each 1 H, $H_2NC=O$); 4.86 (m, H-33).

The following compounds of formula I are obtained in analogous manner in accordance with process variant f):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
40	39[1)]	(c)	na	OMe	NH_2COCOO-	NH_2COCOO-	sb	allyl	OH	sb	cfr; NMR*
41	39,49	(c)	na	OMe	NH_2COCOO-	OtBDMS	sb	Et	OH	sb	cfr; NMR*
42	39,40	(c)	na	OMe	NH_2COCOO-	NH_2COCOO-	sb	Et	OH	sb	cfr

[1)] Stirring is effected for 1 hour at room temperature; column chromatography is effected using an eluant gradient of 3:1 to 1:3;
*^{1}H-NMR: Example 40: see Example 27b; Example 41: see Example 29.

Example 43: 24-Methoxy-33-tert-butyldimethylsilyloxy-FK 506

[Formula I: R_1 = a group (c) wherein R_5 = OMe, R_7 = OtBDMS; R_2 = OMe, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant g), methylation]

1 g **33-tert-butyldimethylsilyloxy-FK 506** is dissolved into a mixture of 50 ml of dichloromethane and 0.04 ml of borotrifluoride etherate previously cooled to 0° to 5°. A solution of 20 ml of an approximately 1 N solution of diazomethane in methylene chloride is then added dropwise in such a manner that the yellow coloration of the solution which initially forms persists for as shortly as possible. The reaction mixture is diluted with acetic acid ethyl ester, successively washed with saturated aqueous sodium hydrogen carbonate solution and water, dried over sodium sulfate, filtered and the solvent is removed under reduced pressure. The **title compound** is obtained as a colourless foamy resin from the residue following column chromatographic purification over silicagel (eluant: acetic acid ethyl ester / n-hexane):
^{1}H-NMR: about 3:1 mixture of conformers:
main conformer: 5.25 (d, J = 8 Hz, H-29); 5.17 (d, J = 7 Hz, H-26); 4.79 (d, J = 10 Hz, H-20); 3.82 (dxd, J = 9 Hz and 1.5 Hz, H-14); 3.42, 3.40, 3.33 and 3.24(4xs, OCH_3); 2.68 (dxd, J = 13 Hz and 8 Hz, H-23);
minor conformer: 3.90 (dxd, J = 9/2,5 Hz, H-14);

The following compounds of formula I are obtained in analogous manner in accordance with process variant g):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
44	43[1)]	(c)	na	OMe	OMe	OtBDMS	sb	allyl	OH	sb	cfr; NMR*

*) ^{1}H-NMR: about 2:1 mixture of conformers: main conformer: 5.22 (d, J = 7Hz, H-26); 4.84 (d, J = 10Hz, H-20); 4.07 (m, H-24); 3.80 (dxd, J = 9Hz and 1.5Hz, H-14); 3.45, 3.44, 3.40 and 3.32 (4xs; OCH_3); 2.78 (dxd, J = 15Hz and .5Hz,H-23); 0.87 (tBu); minor conformer: 4.26 (m, H-24); 3.94 (dxd, J = 9Hz and 2.5Hz, H-14); 0.86 (tBu);
1) Starting from 24-tert-butyldimethylsilyloxy-FK 506.

Example 45: 24-tert-Butyldimethylsilyloxy-33-oxo-FR 520

[Formula I: R_1 = a group (c) wherein R_5 = OMe, R_7 = oxo; R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant h), oxidation]

2 g **24-tert-butyldimethylsilyloxy-FR 520** and 1 g N-methylmorpholin-N-oxide are dissolved in 100 ml of methylene chloride, reacted with 5 g molecular sieve (Molsieb 4A) and the mixture is stirred for 15 minutes at room temperature. 0.15 g tetrapropylammonium perruthenate is added and stirring is continued for 3 more hours at room temperature. The mixture is concentrated, the residue is taken up in acetic acid ethyl ester and the solution successively washed with saturated aqueous sodium hydrogen sulfite solution, saturated aqueous sodium chloride and saturated aqueous copper sulfate solution, the organic phas is dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is

obtained from the residue following column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester).

The following compounds of formula I are obtained in analogous manner in accordance with process variant h):

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
46	45[1)]	(c)	na	OMe	OtBDMS	oxo	sb	Et	OH	sb	cfr
46a	45[2)]	(c)	na	OMe	oxo	OtBDMS	sb	allyl	OH	sb	cfr; NMR*
46b	45	(c)	na	OMe	OtBDMS	oxo	sb	allyl	OH	sb	cfr; NMR*

* Example 46a: ^{13}C-NMR: see Example 15a; Example 46b: ^{1}H-NMR and ^{13}C-NMR: see Example 16b;
1) Starting from 33-tert-butyldimethylsilyloxy-FR 520 (DOS 39 38 754);
2) Starting from 24-tert-butyldimethylsilyloxy-FK 506;
3) Starting from 33-tert-butyldimethylsilyloxy-FK 506;
The compounds of Examples 47 and 50 may be prepared in analogous manner according to process variant h).

Example 47: 24-Oxo-FK 506

[Formula I: R_1 = a group (c) wherein R_6 = OMe, R_7 = OH; R_2 = oxo, single bond in 23,24 position; R_3 = allyl; R_4 = OH, single bond in 10,11 position]

[Process variant deprotection]

3.6 g **24-oxo-33-tert-butyldimethylsilyloxy-FK506** (compound of Example 16b) is dissolved at room temperature into a mixture of 110 ml of acetonitrile and 3 ml of 40 % wt. aqueous hydrofluoric acid and the mixture is stirred at room temperature for 45 minutes. The reaction mixture is diluted with acetic acid ethyl ester, washed successively with saturated aqueous sodium bicarbonate solution and then water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained as a colourless foamy resin following chromatographic purification of the residue over silicagel (eluant: acetic acid ethyl ester / n-hexane 3:2):
^{1}H-NMR: about 1:1 mixture of conformers:
5.80 and 5.60 (s, H-23); 3.44, 3.41, 3.39, 3.38 and 2x3.275 (OCH_3).

The following compounds of formula I are obtained in analogous manner in accordance with process variant deprotection:

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
48	47[1)]	(c)	na	OMe	NH_2CH_2COO–	OH	sb	allyl	OH	sb	cfr; NMR*
49	47[2)]	(c)	na	OMe	NH_2CH_2COO–	absent	db	allyl	OH	sb	cfr; NMR*
50	47[3)]	(c)	na	OMe	OH	oxo	sb	Et	OH	sb	cfr; NMR*
51	47[4)]	(c)	na	OMe	NH_2CH_2COO–	OH	sb	Et	OH	sb	cfr; NMR*
52	47[5)]	(c)	na	OMe	NH_2CH_2COO–	absent	db	Et	OH	sb	cfr; NMR*
53	47[6)]	(c)	na	OMe	$HOCH_2COO$–	OH	sb	allyl	OH	sb	cfr
54	47[7)]	(c)	na	OMe	$HOCH_2COO$–	OH	sb	Et	OH	sb	cfr; NMR*
55	47[8)]	(c)	na	OMe	$HOCH(CH_3)COO$– (S)	OH	sb	Et	OH	sb	cfr; NMR*
56	47[9)]	(c)	na	OMe	OH	NH_2CH_2COO–	sb	Et	OH	sb	cfr
57	47[10)]	(c)	na	OMe	NH_2CH_2COO–	NH_2CH_2COO–	sb	Et	OH	sb	cfr
58	47[11)]	(c)	na	OMe	NH_2CH_2COO–	NH_2CH_2COO–	sb	allyl	OH	sb	cfr
59	47[12)]	(c)	na	OMe	OH	NH_2CH_2COO–	sb	allyl	OH	sb	cfr
60	47[13)]	(c)	na	OMe	NH_2CH_2COO–	OH	sb	allyl	OH	sb	cfr; NMR*
61	47[14)]	(c)	na	OMe	NH_2CH_2COO–	OH	sb	Et	OH	sb	cfr; NMR*
62	47[15)]	(c)	na	OMe	iBuoyloxy	OH	sb	Et	OH	sb	cfr; NMR*
63	47[16)]	(c)	na	OMe	iBuoyloxy	OH	sb	allyl	OH	sb	cfr

Example No.	Analogous to Ex. No.	R_1	R_5	R_6	R_7	R_2	Position 23,24	R_3	R_4	Position 10,11	Physicochemical characterization data
64	47[17]	(a)	I	OMe	na	OH	sb	Et	OH	sb	cfr; **
65a	47[18]	(a)	Cl	OMe	na	OH	sb	allyl	OH	sb	cfr; NMR*
65b	47[18]	(a)	Cl	OMe	na	OH	sb	allyl	absent	db	cfr
66a	47[19]	(a)	Cl	OMe	na	OH	sb	Et	OH	sb	cfr; NMR*
66b	47[19]	(a)	Cl	OMe	na	OH	sb	Et	absent	db	cfr; NMR*
67a	47[20]	(a)	Br	OMe	na	OH	sb	Et	OH	sb	cfr; NMR*
67b	47[20]	(a)	Br	OMe	na	OH	sb	Et	absent	db	cfr
68a	47[21]	(a)	N_3	OMe	na	OH	sb	allyl	OH	sb	cfr; NMR*
68b	47[21]	(a)	N_3	OMe	na	OH	sb	allyl	absent	db	cfr; NMR*
69a	47[22]	(a)	Br	OMe	na	OH	sb	allyl	OH	sb	cfr
69b	47[22]	(a)	Br	OMe	na	OH	sb	allyl	absent	db	cfr
70a	47[23]	(a)	N_3	OMe	na	OH	sb	Et	OH	sb	cfr; NMR*
70b	47[23]	(a)	N_3	OMe	na	OH	sb	Et	absent	db	cfr

1) Starting from the compound of Example 25a;
2) Starting from the compound of Example 25d;
3) Starting from the compound of Example 46 (=16d);
4) Starting from the compound of Example 23;
5) Starting from the compound of Example 26d;
6) Starting from the compound of Example 22;
7) Starting from the compound of Example 24;
8) Starting from the compound of Example 19 or of Example 33;
9) Starting from the compound of Example 26b;
10) Starting from the compound of Example 26c;

11) Starting from the compound of Example 25c;
12) Starting from the compound of Example 25b;
13) Starting from the compound of Example 25a;
14) Starting from the compound of Example 26a;
15) Starting from the compound of Example 34;
16) Starting from the compound of Example 35;
17) Starting from the compound of Example 6a;
18) Starting from the compound of Example 1;
19) Starting from the compound of Example 3;
20) Starting from the compound of Example 4;
21) Starting from the compound of Example 2;
22) Starting from the compound of Example 5;
23) Starting from the compound of Example 6;

*NMR: Example 48: ^{1}H-NMR: about 2:1 mixture of conformers:
5.33 and 5.20 (d/d, J=1 Hz and 1 Hz, H-26); 4.84 (dxdxd, J=5 Hz, 9.5 Hz and 11 Hz, H-33); 3.44 (s, 2H, O=C-CH_2-N-); 3.22 (dxdxd, J=5 Hz, 9.5 Hz and 11 Hz, H-32);

Example 49: ^{1}H-NMR: see Example 18;

Example 50: ^{1}H-NMR: mixture of conformers:
5.8 and 5.6 (s/s, H-23); 5.69 (H-26); 4.38 (d, J=13 Hz, H-6e); 4.19 (t, H-2); 3.80 (dxd, J=9 Hz and 2 Hz, H-14);

Example 51: ^{1}H-NMR: about 2:1 mixture of conformers:
5.34 (d, J=2 Hz, H-26); 4.75 (dxdxd, J=5 Hz, 9 Hz and 10 Hz, H-33); 4.61 (db, J=4 Hz, H-2); 4.44 (db, J=13 Hz, H-6e); 3.45 (s, -CH_2-N);

Example 53: ^{1}H-NMR: see Example 20;
Example 54: ^{1}H-NMR: see Example 32;
Example 55: ^{1}H-NMR: mixture of conformers: main conformer: 1.23 (d, J=7 Hz); 4.30 [dq, J_1=5 Hz, J_2=7 Hz, -COCH(CH_3)OH]; 4.44 (d, br, J=13 Hz, H-6e); 4.61 (d, br, J=4 Hz); 4.78 (ddd, J_1=5 Hz, J_2=5 Hz, J_3=11 Hz, H-33); 5.34 (H-26);
Example 60: ^{1}H-NMR: see Example 48;
Example 61: ^{1}H-NMR: see Example 51;
Example 62: ^{1}H-NMR: see Example 37;
Example 65a: ^{1}H-NMR 4.59 (m, H-33);
^{13}C-NMR: about 2:3 mixture of conformers:
main conformer: 59.1 (C-33; 79.2 (C-32); 97.5 (C-10); 116.4 (C-38); 123.0 (C-20); 135.6 (C-37); 138.4 (C-19); 164.6 (C-8); 168.9 (C-1); 196.4 (C-9); 209.4 (C-22);
Example 66a: ^{1}H-NMR: 4.56 (m, H-33);
Example 66b: ^{1}H-NMR: 2.09 (s, 11-CH_3); 4.5 (bm, H-33);
^{13}C-NMR: about 2:1 mixture of conformers:
main conformer: 56.2 (C-33); 80.6 (C-32); 116.4 (C-38); 122.9 (C-20); 124.8 (C-11); 129.5 (C-29); 131.9 (C-28): 135.8 (C-37); 140.0 (C-19); 142.9 (C-10); 166.7 (C-8); 168.7 (C-1); 188.0 (C-9); 212.4 (C-22);
minor conformer: 56.1 (C-33); 80.6 (C-32); 116.5 (C-38); 123.6 (C-20); 126.4 (C-11); 128.5 (C-29); 131.8 (C-28); 135.6 (C-37); 137.4 (C-19); 144.1 (C-10); 166.5 (C-8); 169.5 (C-1); 184.8 (C-9); 213.3 (C-22);
Example 67a: ^{1}H-NMR: 4.44 (d, J=13 Hz, H-6 eq.); 4.60 (d, J=4 Hz, H-2); 4.70 (sb, H-33);
Example 68a: ^{1}H-NMR: 4.07 (m, $w_{1/2}$ = 8 Hz, H-33);
Example 68b: ^{1}H-NMR: about 2:1 mixture of conformers: 4.06 (m, H-33); 2.09 and 1.94 (2s, 11-CH_3);
Example 70a: ^{1}H-NMR: about 5:4 mixture of conformers: 5.60 resp. 5.79 (s resp. s, H-23); 5.70 resp. 5.66 (d, J=3 Hz resp. d, J=3 Hz, H-26); 4.38 (d, J=13 Hz, H-6e); 4.15 (t, H-2); 3.80 (dxd, J=9 Hz and 2 Hz, H-14).

** Iodine analyis: theor.: 14.06 %; found: 13.57 %.

The compounds of Examples 10a, 11a, 12, 13, 27a and 28a may be prepared in analogous manner according to process variant deprotection.

Example 71: 24-tert-Butyldimethylsilyloxy-29-des-(4-hydroxy-3-methylcyclohexyl)-29-(3-formylcyclopentyl)-FR 520

[Formula I: R_1 = a group (d); R_2 = OtBDMS, single bond in 23,24 position; R_3 = Et; R_4 = OH, single bond in 10,11 position]

[Process variant protection]

A solution of 1.2 g **29-des-(4-hydroxy-3-methylcyclohexyl)-29-(3-formylcyclopentyl)-FR 520** - (compound of Example 12), 1.5 g tert-butyldimethylsilyl chloride and 0.8 g imidazole in 20 ml of dry dimethylformamide is stirred for 15 hours at room temperature and thereafter partitioned between 1 N hydrochloric acid solution and acetic acid ethyl ester. The organic phase is separated, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated under reduced pressure. The **title compound** is obtained from the residue as a colourless foamy resin following column chromatography over silicagel (eluant: n-hexane / acetic acid ethyl ester):
^{1}H-NMR: mixture of rotamers: 9.65 (d, J = 2 Hz, CHO); 539 (d, J = 9 Hz, H-29); 5.01 (d, J = 7.5 Hz, H-26); 4.81 (d, J = 10 Hz, H-20); 3.82 (dxd, J = 9/2 Hz, H-24).

The compounds of Examples 1 to 9, 16a to 16d, 19, 21 to 26d, 29, 30, 34, 35, 38, 39, 41 and 43 to 46b may be prepared in analogous manner according to process variant protection.

The compounds of the invention possess pharmacological activity. They are indicated for use as pharmaceuticals.

In particular they possess antiinflammatory, and immunosuppressant and antiproliferative activity.

Antiinflammatory activity may e.g. be determined in the following test methods:

1. Oxazolone allergic contact dermatitis in the mouse in vivo upon topical application: the test method is as described in F.M. Dietrich and R. Hess, Int. Arch. Allergy 38 (1970) 246-259.
The compounds elicit in this test an activity between about 15 % and about 68 % upon topical administration at a concentration of about 0.01 %.

2. DNFB allergy (swine): the test method is as described in e.g. EP 315978.
Topical application of a 1.2 % formulation of the compounds repeated twice results in from about 36 % to about 40 % inhibition of the inflammatory reaction.

Immunosuppressant and antiproliferative activity may e.g. be determined in the following test methods:

1. Proliferative response of lymphocytes to allogen stimulation in the mixed lymphocyte reaction (MLR) in vitro: T. Meo, "The MLR in the Mouse", Immunological Methods, L. Lefkovits and B. Pernis, Eds., Academic Press, N.Y. (1979), 227-239.
The compounds elicit in this test (IC_{50}) suppression of mixed lymphocytes at a dosage of from about < 0.0008 µg/ml to about 0.09 µg/ml.

2. Inhibition of the primary humoral immune response to sheep erythrocytes in vitro: the test method is as described in R.I. Mishell and R.W. Dutton, Science 153 (1966) 1004-1006; R.I. Mishell and R.W. Dutton, J. Exp. Med. 126 (1967) 423-442.
The compounds are active in this test with an IC_{50} of from about 0.0024 µg/ml to about 0.32 µg/ml.

3. Inhibition of proliferation of human keratinocytes: the test method is as described in e.g. EP 315978.
The compounds are active in this test at concentrations of from about 1 µg/ml to about 10 µg/ml resulting in a inhibition of from about 30 % to about 90 %.

The compounds of the invention in free form and where such forms exist in pharmaceutically acceptable salt form are therefore indicated as antiinflammatory and as immunosuppressant and antiproliferative agents for use in the prevention and treatment of inflammatory conditions and of conditions requiring immunosuppression, such as

a) the prevention and treatment of
- resistance in situations of organ or tissue transplantation, e.g. of heart, kidney, liver, bone marrow and skin,
- graft-versus-host disease, such as following bone marrow grafts,
- autoimmune diseases such as rheumatoid arthritis, systemic Lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, Myasthenia gravis, diabetes type I and uveitis,

- cutaneous manifestations of immunologically-mediated illnesses;

b) the treatment of inflammatory and hyperproliferative skin diseases, such as psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and acne; and

c) Alopecia areata.

The compounds may be administered systemically or topically.

For these indications the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.15 mg/kg to about 1.5 mg/kg animal body weight. An indicated daily dosage in the larger mammal is in the range from about 0.01 mg to about 100 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

For topical use satisfactory results are obtained with local administration of a 1-3 % concentration of active substance several times daily, e.g. 2 to 5 times daily. Examples of indicated galenical forms are lotions, gels and creams.

The compounds of the invention may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or topically, e.g. in the form of lotions, gels or creams.

Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms contain, for example, from about 0.0025 mg to about 50 mg of active substance.

Topical administration is e.g. to the skin. A further form of topical administration is to the eye, for the treatment of immune-mediated conditions of the eye, such as: auto-immune diseases, e.g. uveitis, keratoplasty and chronic keratitis; allergic conditions, e.g. vernal conjunctivitis; inflammatory conditions and corneal transplants, by the topical administration to the eye surface of a compound of the invention in a pharmaceutically acceptable ophthalmic vehicle.

The ophthalmic vehicle is such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, e.g. the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera.

The pharmaceutically acceptable ophthalmic vehicle may be e.g. an ointment, vegetable oil, or an encapsulating material.

Whilst the antiinflammatory and immunosuppressant and antiproliferative activity is the main activity of the compounds of the invention they also possesses some degree of activity in increasing sensitivity to, or in increasing the efficacy of, chemotherapeutic drug therapy.

This activity may e.g. be determined according to the test methods described in EP 360760.

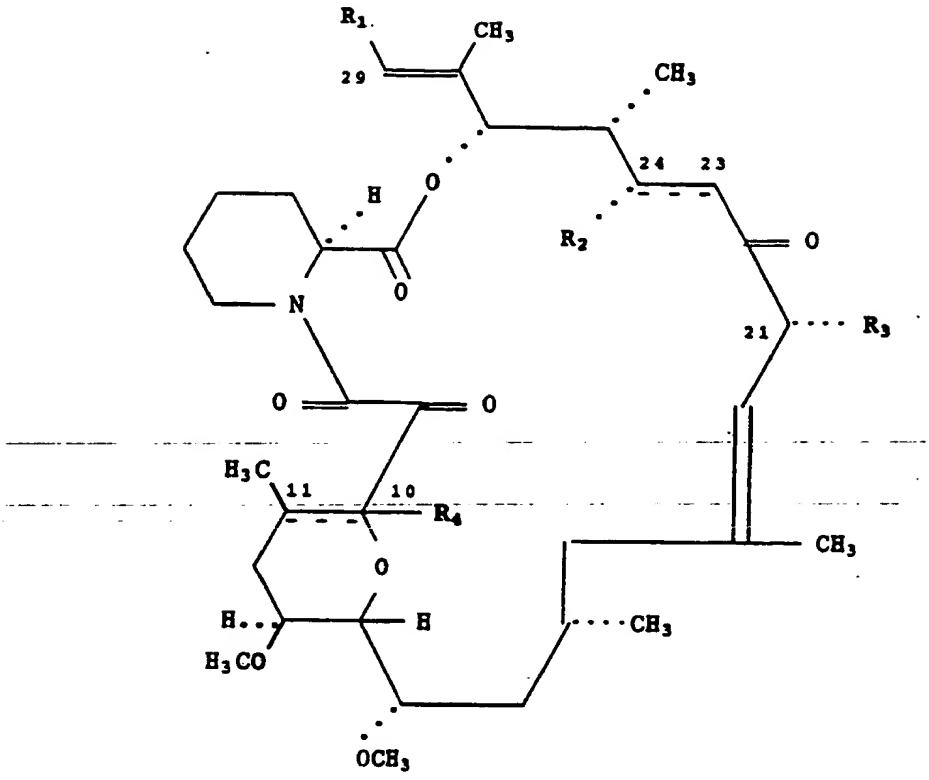
The compounds of the invention are therefore indicated for use in reversing chemotherapeutic drug resistance of varying types, e.g. acquired or innate, or in increasing sensitivity to administered drug therapy, e.g. as a means of reducing regular chemotherapeutic dosage levels, for example in the case of anti-neoplastic or cytostatic drug therapy, as a means of decreasing overall drug toxicity and, more especially, as a means of reversing or reducing resistance, including both inherent and acquired resistance, to chemotherapy.

Preferred in the above indications are the following compounds of the invention:

- 29-des-(4-hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520 (compound of Example 12);
- 33-aminooxalyloxy-FR 520 (compound of Example 28a);
- FR 520-33-glycolate (compound of Examples 32 and 54);
- 33-isobutanoyloxy-FR 520 (compound of Examples 37 and 62); and
- 33-epi-33-chloro-PR 520 (compound of Example 66a).

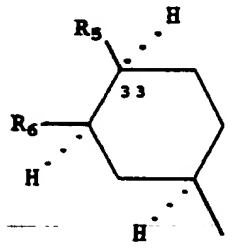
Claims

1. A compound of formula I



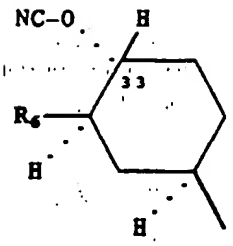
I

wherein
either R_1 is a group (a) of formula

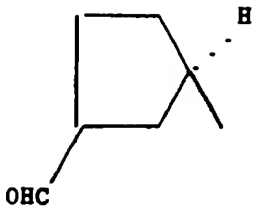


(a)

wherein R_5 is chloro, bromo, iodo or azido and R_6 is hydroxy or methoxy;
R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;
or R_1 is a group (b) or (d) of formula

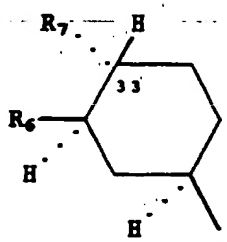


(b) and



(d)

wherein R_6 is as defined above;
R_2 is as defined above; and
R_4 is hydroxy and there is a single bond in 10,11 position;
or R_1 is a group (c) of formula



(c)

wherein R_6 is as defined above and
R_7 is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; isobutanoyloxy; aminooxalyloxy; R_8R_9CHCOO- wherein R_8 is optionally protected hydroxy or optionally protected amino and R_9 is hydrogen or methyl; or p-tolyloxythiocarbonyloxy;
R_2 is oxo and there is a single bond in 23,24 position; absent and there is a double bond in 23,24 position; or is optionally protected hydroxy, methoxy, methylthiomethoxy, isobutanoyloxy, aminooxalyloxy or R_8R_9CH COO- wherein R_8 and R_9 are as defined above, and there is a single or a double bond in 23,24 position;
whereby for group (c)
1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_2 is other than absent and other than unprotected hydroxy or methoxy, and
there is a single bond in 23,24 position;
2) when R_6 is methoxy and R_7 is methylthiomethoxy
then R_2 is other than absent and other than unprotected hydroxy;
3) when R_6 is methoxy and R_7 is protected hydroxy
then R_2 is other than optionally protected hydroxy; and
4) when R_6 is hydroxy
then R_7 is other than optionally protected hydroxy; and
R_4 is hydroxy and there is a single bond in 10,11 position; and R_3 is methyl, ethyl, n-propyl or allyl;
in free form or, where such forms exist, in salt form.

2. A compound according to claim 1 which is a **compound Ip_1**,
i.e. a compound of formula I wherein
R_1 is a group (a) wherein R_6 is methoxy and
either R_5 is chloro or bromo and
R_4 is hydroxy and there is a single bond in 10,11 position
or R_5 is azido and
R_4 is hydroxy and there is a single bond in 10,11 position or absent and there is a double bond in 10,11 position;
R_2 is optionally protected hydroxy and there is a single or a double bond in 23,24 position; and
R_3 is as defined in claim 1;
in free form or, where such forms exist, in salt form.

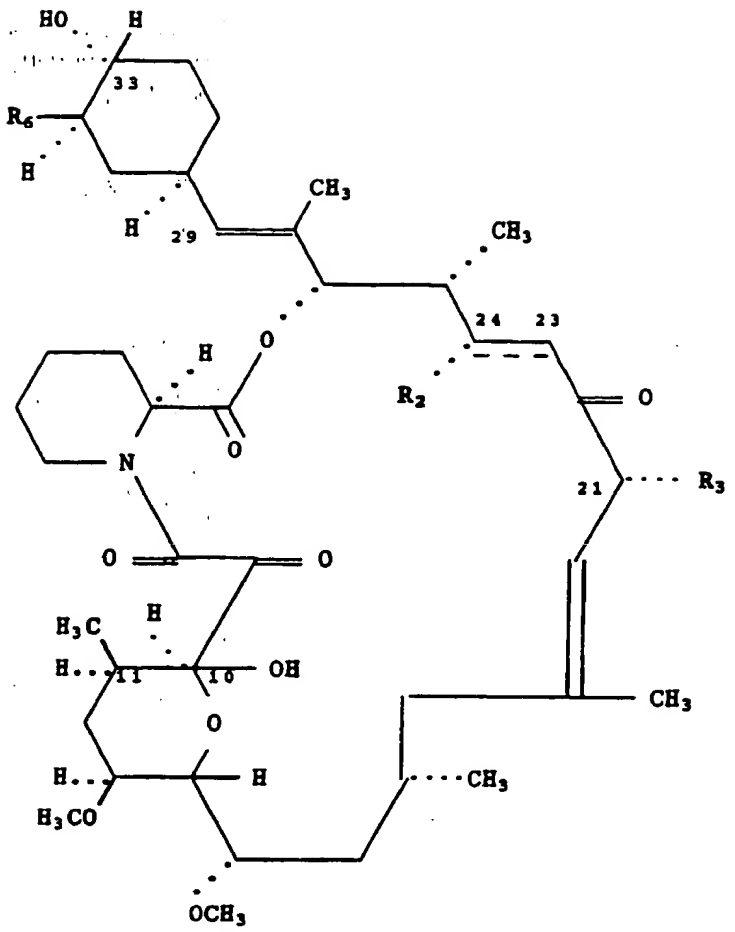
3. A compound according to claim 1 which is a **compound Ip_2**,
i.e. a compound of formula I wherein

R_1 is a group (c) wherein R_6 is methoxy and R_7 is oxo; optionally protect d hydroxy; methoxy; methylthiomethoxy; aminooxalyloxy; R_8CH_2COO- wherein R_8 is optionally protected amino; or p-tolyloxythiocarbonyloxy;
R_2 is absent and there is a double bond in 23,24 position; or optionally protected hydroxy, methoxy, methylthiomethoxy or aminooxalyloxy and there is a single or double bond in 23,24 position;
whereby
1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_2 is other than absent and other than unprotected hydroxy or methoxy, and
there is a single bond in 23,24 position;
2) when R_7 is methylthiomethoxy
then R_2 is other than absent and other than unprotected hydroxy; and
3) when R_7 is protected hydroxy
then R_2 is other than optionally protected hydroxy; and
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is as defined in claim 1;
in free form or, where such forms exist, in salt form.

4. A compound according to claim 1 which is a **compound Ip_3**,
i.e. a compound of formula I wherein
R_1 is a group (b) wherein R_6 is methoxy,
R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is as defined in claim 1;
in free form or, where such forms exist, in salt form.

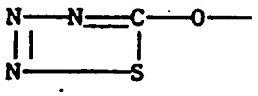
5. A compound according to claim 1 which is a **compound Ip_4**,
i.e. a compound of formula I wherein
R_1 is a group (d),
R_2 is optionally protected hydroxy and there is a single bond in 23,24 position; or absent and there is a double bond in 23,24 position;
R_4 is hydroxy and there is a single bond in 10,11 position; and
R_3 is as defined in claim 1;
in free form or, where such forms exist, in salt form.

6. A process for the preparation of a compound according to claim 1 comprising
a) for the preparation of a compound of formula I wherein
R_1 is a group (a) as defined in claim 1,
R_2 and R_3 are as defined in claim 1 and
R_4 is hydroxy (i.e. a **compound Ia**),
replacing under simultaneous epimerization the hydroxy group by chlorine, bromine, iodine or azido in a corresponding compound having unprotected hydroxy in 33 position (i.e. a **compound IIa**, of formula IIa



IIa

wherein R_2 and R_3 are as defined above under formula I and R_6 is hydroxy or methoxy);
b) for the preparation of a compound of formula I wherein
R_1 is a group (b) as defined in claim 1,
R_2 and R_3 are as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ib**),
treating a corresponding compound IIa with cyanogen bromide in the presence of a base or
treating a corresponding compound IIa with thiophosgene, reacting the resultant product with an inorganic azide and allowing the resultant unstable intermediate having a group



in 33 position (i.e. a **compound IIb**)
to decompose to a corresponding compound Ib;
c) for the preparation of a compound of formula I wherein
R_1 is a group (d) as defined in claim 1,
R_2 and R_3 are as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ic**),
treating a corresponding compound Ib with an acid having a non-nucleophilic anion;

d) for the preparation of a compound of formula I wher in
R_1 is a group (c) wherein R_6 is as defined in claim 1,
one of R_2 and R_7 is oxo or methylthiomethoxy and the other is protect d hydroxy,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Id**),
treating a corresponding compound wherein
one of the substituents in 24 and 33 position is hydroxy and the other is protected hydroxy,
(i.e. a **compound IIc**)
with dimethylsulfoxide and acetanhydride;
e) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein
R_6 is as defined in claim 1 and
R_7 is isobutanoyloxy, aminooxalyloxy, R_8R_9CHCOO- as defined in claim 1 or p-tolyloxythiocarbonyloxy,
R_2 and R_3 are as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ie**),
appropriately acylating a corresponding compound IIa;
f) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein
R_6 is as defined in claim 1 and
R_7 is aminooxalyloxy,
R_2 is optionally protected hydroxy or is aminooxalyloxy,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound If**),
treating with an appropriate oxalyl derivative and thereafter with ammonia a corresponding compound having an optionally protected hydroxy group in 33 position and a protected hydroxy group in 24 position (i.e. a **compound IId**);
g) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined in claim 1,
R_2 and R_7 are as defined in claim 1 with the proviso that one of R_2 and R_7 is methoxy,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ig**),
methylating a corresponding compound having a hydroxy group in 24 or 33 position
(i.e. a **compound IIe**);
h) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined in claim 1,
R_2 and R_7 are as defined in claim 1 with the proviso that one of R_2 and R_7 is oxo,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ih**),
oxidizing a corresponding compound having a hydroxy group in 24 or 33 position
(i.e. a **compound IIf**); and
- when a resultant compound of formula I has a protected hydroxy and/or a protected amino group,
optionally splitting off the protecting group(s) to give a corresponding compound of formula I having one or more unprotected hydroxy and/or unprotected amino group(s)
(i.e. a **compound Ij**),
whereby when R_1 is a group (a), a water molecule may be simultaneously split off and a compound of formula I is obtained wherein
R_1 is a group (a) as defined in claim 1,
R_2 is unprotected hydroxy and there is a single or double bond in 23,24 position; and
R_4 is absent and there is a double bond in 10,11 position (i.e. a **compound Il**); or
- optionally protecting a unprotected hydroxy and/or unprotected amino group in a resultant compound of formula I as appropriate to give a corresponding compound of formula I having one or more protected hydroxy and/or protected amino groups(s) (i.e. a **compound Ik**);
and recovering the resultant compound of formula I in free form and, where such forms exist, in salt form.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 in-free form or, wher such forms exist, in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable carrier or diluent.

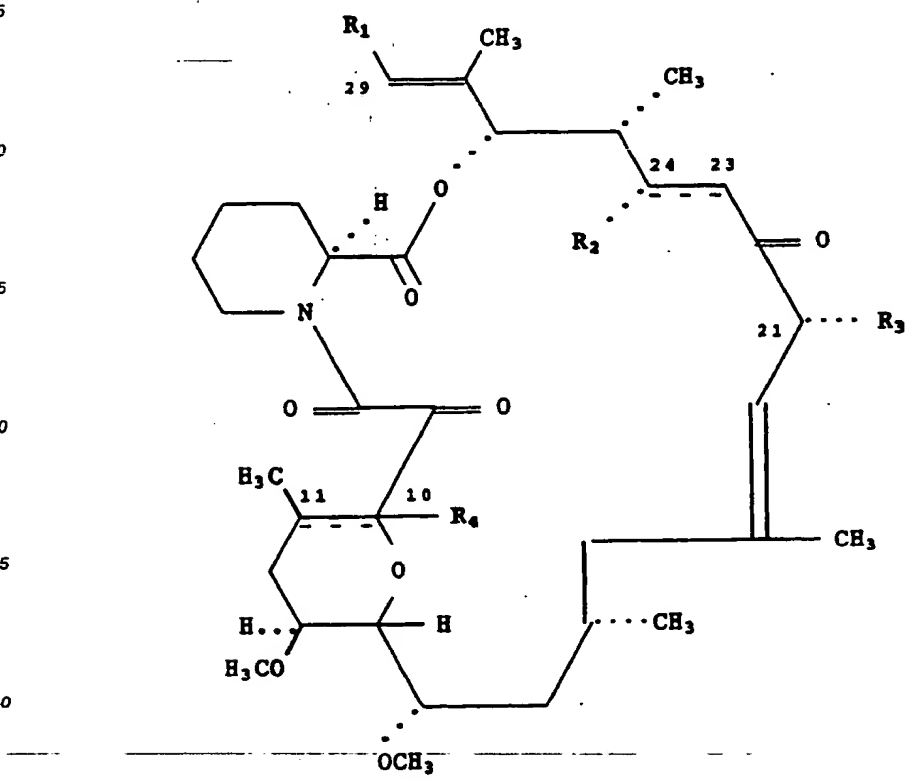
8. A compound according to any one of claims 1 to 5 in free form or, where such forms exist, in pharmaceutically acceptable salt form, for use as a pharmaceutical.

9. A compound according to claim 8 for use in the preparation of a pharmaceutical composition by mixing with a pharmaceutically acceptable carrier or diluent.

10. A process for the preparation of a pharmaceutical composition comprising mixing a compound according to any one of claims 1 to 5 in free form or, where such forms exist, in pharmaceutically acceptable salt form, with a pharmaceutically acceptable carrier or diluent.

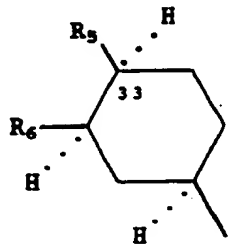
Claims for the following Contracting States: ES, GR

1. A process for the preparation of a compound of formula I



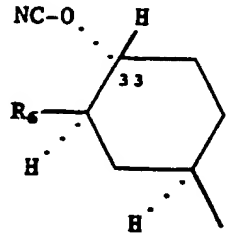
I

wherein
either R_1 is a group (a) of formula



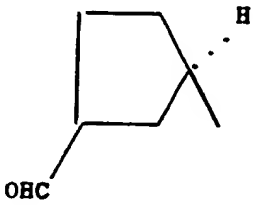
(a)

wherein R_5 is chloro, bromo, iodo or azido and
R_6 is hydroxy or methoxy;
R_2 is oxo and there is a single bond in 23,24 position; optionally protected hydroxy and there is a single or a double bond in 23,24 position; or absent and there is a double bond in 23,24 position; and
R_4 is hydroxy and there is a single bond in 10,11 position; or absent and there is a double bond in 10,11 position;
or R_1 is a group (b) or (d) of formula



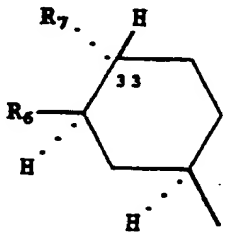
(b)

and



(d)

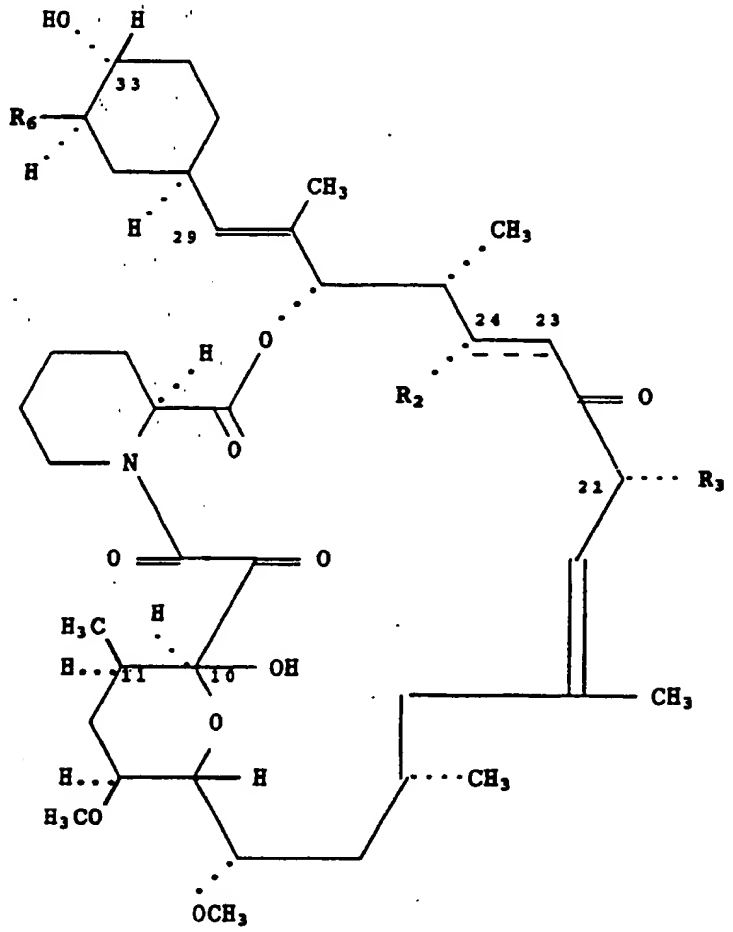
wherein R_6 is as defined above;
R_2 is as defined above; and
R_4 is hydroxy and there is a single bond in 10,11 position;
or R_1 is a group (c) of formula



(c)

wherein R_6 is as defined above and
R_7 is oxo; optionally protected hydroxy; methoxy; methylthiomethoxy; isobutanoyloxy; aminooxalyloxy; R_8R_9CHCOO- wherein R_8 is optionally protected hydroxy or optionally protected amino and R_9 is hydrogen or methyl; or p-tolyloxythiocarbonyloxy;
R_2 is oxo and there is a single bond in 23,24 position; absent and there is a double bond in 23,24 position; or is optionally protected hydroxy, methoxy, methylthiomethoxy, isobutanoyloxy, aminooxalyloxy or R_8R_9CH COO- wherein R_8 and R_9 are as defined above, and there is a single or a double bond in 23,24 position; whereby for group (c)
1) when R_7 is oxo, unprotected hydroxy or methoxy
then R_2 is other than absent and other than unprotected hydroxy or methoxy, and
there is a single bond in 23,24 position;
2) when R_6 is methoxy and R_7 is methylthiomethoxy
then R_2 is other than absent and other than unprotected hydroxy;
3) when R_6 is methoxy and R_7 is protected hydroxy
then R_2 is other than optionally protected hydroxy; and
4) when R_6 is hydroxy
then R_7 is other than optionally protected hydroxy; and
R_4 is hydroxy and there is a single bond in 10,11 position; and R_3 is methyl, ethyl, n-propyl or allyl;
in free form or, where such forms exist, in salt form,
comprising
a) for the preparation of a compound of formula I wherein
R_1 is a group (a) as defined in claim 1,
R_2 and R_3 are as defined in claim 1 and
R_4 is hydroxy (i.e. a compound Ia),

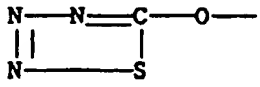
replacing under simultaneous epimerization the hydroxy group by chlorine, bromine, iodine or azido in a corresponding compound having unprotected hydroxy in 33 position (i.e. a **compound IIa**, of formula IIa



IIa

wherein R_2 and R_3 are as defined above under formula I and R_6 is hydroxy or methoxy);

b) for the preparation of a compound of formula I wherein
R_1 is a group (b) as defined in claim 1,
R_2 and R_3 are as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ib**),
treating a corresponding compound IIa with cyanogen bromide in the presence of a base or
treating a corresponding compound IIa with thiophosgene, reacting the resultant product with an inorganic azide and allowing the resultant unstable intermediate having a group



in 33 position (i.e. a **compound IIb**)
to decompose to a corresponding compound Ib;

c) for the preparation of a compound of formula I wherein
R_1 is a group (d) as defined in claim 1,
R_2 and R_3 are as defined in claim 1 and

R_4 is hydroxy
(i.e. a **compound Ic**),
treating a corresponding compound Ib with an acid having a non-nucleophilic anion;
d) for th preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined in claim 1,
one of R_2 and R_7 is oxo or methylthiomethoxy and the other is protected hydroxy,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Id**),
treating a corresponding compound wherein
one of the substituents in 24 and 33 position is hydroxy and the other is protected hydroxy,
(i.e. a **compound IIc**)
with dimethylsulfoxide and acetanhydride;
e) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein
R_6 is as,defined in claim 1 and
R_7 is isobutanoyloxy, aminooxalyloxy, R_8R_9CHCOO- as defined in claim 1 or p-tolyloxythiocarbonyloxy,
R_2 and R_3 are and defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ie**), appropriately acylating a corresponding compound IIa;
f) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein
R_6 is as defined in claim 1 and
R_7 is aminooxalyloxy,
R_2 is optionally protected hydroxy or is aminooxalyloxy,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound If**),
treating with an appropriate oxalyl derivative and thereafter with ammonia a corresponding compound having an optionally protected hydroxy group in 33 position and a protected hydroxy group in 24 position
(i.e. a **compound IId**);
g) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined in claim 1,
R_2 and R_7 are as defined in claim 1 with the proviso that one of R_2 and R_7 is methoxy,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ig**),
methylating a corresponding compound having a hydroxy group in 24 or 33 position
(i.e. a **compound IIe**);
h) for the preparation of a compound of formula I wherein
R_1 is a group (c) wherein R_6 is as defined in claim 1,
R_2 and R_7 are as defined in claim 1 with the proviso that one of R_2 and R_7 is oxo,
R_3 is as defined in claim 1 and
R_4 is hydroxy
(i.e. a **compound Ih**),
oxidizing a corresponding compound having a hydroxy group in 24 or 33 position
(i.e. a **compound IIf**); and
- when a resultant compound of formula I has a protected hydroxy and/or a protected amino group,
optionally splitting off the protecting group(s) to give a corresponding compound of formula I having one or more unprotected hydroxy and/or unprotected amino group(s)
(i.e. a **compound Ij**),
whereby when R_1 is a group (a), a water molecule may be simultaneously split off and a compound of formula I is obtained wherein
R_1 is a group (a) as defined in claim 1,
R_2 is unprotected hydroxy and there is a single or double bond in 23,24 position; and
R_4 is absent and there is a double bond in 10,11 position (i.e. a **compound Il**); or
- optionally protecting an unprotected hydroxy and/or unprotected amino group in a r sultant compound of formula I as appropriate to give a corresponding compound of formula I having one or mor protected

hydroxy and/or protected amino groups(s) (i.e. a compound Ik);
and recovering the resultant compound of formula I in free form and, where such forms exist, in salt form.
2. A process according to claim 1 for the preparation of the compound according to claim 1 which is 29-des-(4-hydroxy-3-methoxycyclohexyl)-29-(3-formylcyclopentyl)-FR 520 (compound of Example 12).
3. A process according to claim 1 for the preparation of the compound according to claim 1 which is 33-aminooxalyloxy-FR 520 (compound of Example 28a) in free form or in salt form.
4. A process according to claim 1 for the preparation of the compound according to claim 1 which is FR 520-33-glycolate (compound of Examples 32 and 54).
5. A process according to claim 1 for the preparation of the compound according to claim 1 which is 33-isobutanoyloxy-FR 520 (compound of Examples 37 and 62).
6. A process according to claim 1 for the preparation of the compound according to claim 1 which is 33-epi-33-chloro-FR 520 (compound of Example 66a).
7. A process for the preparation of a pharmaceutical composition comprising mixing a compound of formula I as defined in claim 1 in free form or, where such forms exist, in pharmaceutically acceptable salt form, with a pharmaceutically acceptable carrier or diluent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90810854.1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 109, 1987 H. TANAKA et al. "Structure of FK 506:"A novel immunosupressant isolated from Streptomyces"" pages 5031-5033 * Page 5031 *	1,7-10	C 07 D 498/18 A 61 K 31/33 //(C 07 D 498/18 C 07 D 311:00 C 07 D 273:00 C 07 D 221:00)
A	EP - A2 - 0 184 162 (FUJISAWA PHARM.CO.LTD.) * Claims 1-18 *	1-10	
A	EP - A2 - 0 227 355 (THE UNIVERSITY OF KANSAS) * Pages 2-4; claims *	1-10	
A	EP - A1 - 0 323 042 (FISONS PLC.) * Pages 3,7; claims *	1-8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 D 498/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
WIEN	17-01-1991	JANISCH

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)